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OCCURRENCE OF GLIOMA OF RETINA AND BRAIN IN COLLATERAL LINES IN SAME FAMILY

GENETICS OF GLIOMA

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NEWARK, N J

Heredity depends on the intrinsic factors, the genes, and on extrachromosomal influences. Mendelian inheritance is through the chromosomes, and the various traits are carried by the hypothetical biochemical units called genes. The factor of heredity in malignant tumors is of minor importance, with the exception of glioma and neurofibromatosis (von Recklinghausen's disease), in which the hereditary influence is generally recognized and accepted. In addition to these two types of tumors, Lehmann¹ stated that polyposis of the rectum is irregularly dominant, a precancerous condition, with a possibility of development into cancer in 75 per cent of cases, and that xeroderma pigmentosum has a recessive inheritance, with consanguinity in 25 per cent of cases. Xeroderma pigmentosum, with an inborn excess of porphyrins, like polyposis of the rectum, represents a precancerous state, a hereditary hypersensitiveness of the skin to sunlight, especially the ultraviolet rays, resulting in development of carcinoma of the skin, even in childhood. The aforementioned tumors occurring in man have in common that the role of heredity is proved. Among animals, the adenocarcinoma of mice is strikingly hereditary, and in *Drosophila* two kinds of spontaneous tumors are recognized—melanoma, with a recessive gene in the X chromosome, and a benign growth, with a recessive gene in the third chromosome. In contrast to retinoblastoma, in which, according to Wells,² the hereditary factor is conspicuous, are other types of tumors which tend to be congenital or to appear in early infancy without any hereditary factor. Among these are mixed malignant renal neoplasm (Wilms's tumor), neuroblastoma of the adrenal medulla and other parts of the sympathetic nervous system, congenital hepatic hemangioendothelioma, congenital

sarcoma, endothelioma, melanoma, tumors of the testis, chordoma and the leukemias.

Weller³ pointed out that from the standpoint of the study of the intrinsic factors in malignant growths gliomas have a distinct advantage over carcinomas. The hereditary disposition in families with carcinoma is often obscured by death at any time prior to the physiologic limit of life. The evidence for the hereditary factor in gliomas occurring in infancy or in early childhood, on the other hand, is limited only by their occurrence in stillborn children and in children dying in early infancy.

Gliomas are relatively rare. According to Leber⁴ the incidence was less than 0.04 per cent in a large statistical series, and according to Hemmes it was 1 in 24,000 living births. A recent review of the entire literature up to 1943 has been made by Benedict and Parkhill.⁵ In the majority of the articles in the literature sporadic cases are considered, but even the early observers noted the familial trend. Von Lerche (1821) was the first to report an instance of such a trend, that of a family of 7 children, in which 3 boys and 1 girl had retinal glioma. Leber,⁴ in his masterful monograph on retinal diseases, mentioned 15 families with 2 affected children, 6 families with 3 affected children, 4 families with 4 affected children, 1 family with 5 affected children, 1 family with 8 affected children and 1 family with 10 affected children. A review of cases of multiple occurrence shows that Newton reported a family with 10 affected children (3 with unilateral and 7 with bilateral retinal glioma) out of 16, Thompson and Knapp, one with 5 affected children out of 14, Calderini, one with 3 affected children out of 14, Leber.

3 Weller, C. V. The Inheritance of Retinoblastoma and Its Relationship to Practical Eugenics, *Cancer Research* 1:517, 1941.

4 Leber, T. Die Krankheiten der Netzhaut. Das Gliom, in Graefe, A., and Saemisch, T. *Handbuch der gesamten Augenheilkunde*, ed 2, Leipzig, W. Engelmann, 1916, vol 7 A, p 1723.

5 Benedict, W. L., and Parkhill, E. M. Glioma of the Retina in Successive Generations, *Am J Ophthalm* 26:511, 1943.

From the Ophthalmic Department and Laboratory of the Beth-Israel Hospital.

1 Lehmann, W. Kritische Uebersicht Krebs und Vererbung, *Med Klin* 38:567, 1942.

2 Wells, H. G. Occurrence and Significance of Congenital Malignant Neoplasms, *Arch Path* 30:535 (Aug) 1940.

one with 3 affected children out of 9, Maher, one with 3 affected children out of 3, Wilson, one with 8 affected children out of 18, von Leiche, one with 4 affected children out of 7, de Gouvêa, one with 2 affected children out of 7, von Graefe, one with 2 affected children out of 7, Marshall, one with 3 affected out of 6, Macgregor, one with 3 affected children (bilateral glioma) out of 5, Cirincione and Calderaro, each a family with 4 affected children out of 5, Schonemann, a family with 2 affected children out of 3, Valenti, Fuchs, Snell and von Hoffmann, each a family with 2 affected children out of 3, Sichel, a family with 4 affected children out of 4, Snell, 2 affected children, Steinhaus and Owen, each a family with 2 affected children out of 2, Dabney, a family with 3 affected children out of 3 (2 with bilateral and 1 with unilateral glioma), Comas, a family with 5 affected children out of 11, and Weller, a family with 6 affected children out of 10 (2 with bilateral glioma). The familial occurrence was reported by Adam in 3 families, each of them with 2 afflicted children. In this connection, I wish to mention a family of 4 children in which I observed 4 afflicted children (2 with bilateral and 2 with unilateral involvement). One of the most interesting observations is that of Townsend. A Negro woman had a daughter with glioma of the retina. The mother gave birth to 2 daughters by another father, both the children had glioma. The occurrence of families with retinoblastoma, the expression of horizontal inheritance, has been known for many years and points to the hereditary character of glioma, but the majority of cases of this tumor are sporadic, without similar cases either in the ascendants or in the descendants. Hemmes found no familial occurrence in 48 cases, Bucklers, none in 49 cases, Stock, none in 28 cases, Sabugin, none in 14 cases (of sisters and brothers, but not parents), and Davenport, none in 27 cases. Reiser⁶ discovered 1 case in 16 families, with a total of 64 children, Griffith and Sorsby,⁷ tabulating the glioma material of the Royal Eye Hospital, in London, between 1894 and 1943, discovered 53 isolated cases and 6 cases occurring within 1 family in three successive generations. Leber reported on 25 families with multiple occurrence of glioma, mostly among sisters and brothers, and Bell,⁸ on 36 families. Hemmes

increased the number (including those reported on by Fietta, van der Hoeve and Mayer-Riemsloh) to 39 families. According to Reiser, there are recorded in the literature about 50 families with multiple occurrence of glioma, this number includes the 467 cases of Wintersteiner. Considering that about 1,000 cases have been reported in the literature, one has to assume that cure through operation has been attained in 40 or 50 per cent, so that a large number of patients with healed glioma reach the reproductive age, this is in apparent contradiction to the known cases of hereditary transmission.

The multiple occurrence of retinal glioma in the same family and, similarly, the transmission of glioma to the offspring in successive generations were known, but only recently has the vertical familial distribution and the collateral mode of inheritance been appreciated. Transmission from generation to generation, the so-called vertical inheritance, is one of the most important factors in the heredity of disease. Von Graefe was the first to report the transmission of glioma through two generations. De Gouvêa enucleated the right eye of a boy at the age of 2 years, he survived and 2 of his 7 children were afflicted with bilateral glioma. According to Owen, in Bowman's case the father's left eye was enucleated at the age of 5 years, his son had glioma at the age of 3 years, and 2 children of the father's sister were similarly afflicted. In the family reported by von Hoffmann the mother's left eye was enucleated at the age of 2 years, and twenty-eight years later the first son had bilateral glioma, the second son, similarly, had bilateral glioma at the age of 4 months, and the third child is still free of glioma, at the age of 7 months. Steinhaus and Caspar independently described the occurrence of glioma in a mother and daughter. Griffith observed 2 families with glioma. In the first family, the mother had had one eye removed at the age of 9 months, and 4 of her 7 children had bilateral glioma, in the second family, the mother lost one eye, and 3 of her 4 children were afflicted (1 with bilateral and 2 with unilateral glioma). Taylor observed a child with glioma whose mother lost one eye in childhood, presumably of glioma. In the case of de Haas a child with bilateral glioma was the offspring of a father whose right eye was enucleated for the same condition. In Pockley's case both the father's eyes had been lost on account of glioma, and he had a child with bilateral glioma. In the latter case there was not only vertical but horizontal inheritance, as the father was identified with the family reported on by Maher, in which

6 Reiser, K. A. Bemerkungen zur Erblchkeitsfrage beim Glioma retinae, *Klin Monatsbl f Augenh* 99 350, 1937.

7 Griffith, A. D., and Sorsby, A. The Genetics of Retinoblastoma, *Brit J Ophth* 28 279, 1944.

8 Bell, J. The Treasury of Human Inheritance, London, Cambridge University Press, 1922, vol 2, pt 1.

both sisters had bilateral glioma. In the family reported by Traquan the father's left eye had been enucleated by Argyll Robertson for tumor (apparently glioma) at the age of 6 months, the first child was stillborn, and the second exhibited bilateral, and the third unilateral, glioma. In the family reported by Sym, one of the father's eyes was enucleated by Argyll Robertson for a similar reason, the first child was stillborn, the second and third children died of bilateral glioma at the age of 4 years, and the fourth child, a girl, was still normal, at the age of 3 years. Fietta and Odinzow described a case of transmission from mother to daughter, in the family recorded by van der Hoeve the father had unilateral glioma, and 2 of his 12 children had glioma duplex. In the family reported by Letchworth the father lost one eye, and of his 5 children, 1 was stillborn and 3 had glioma (2 bilateral and 1 unilateral). Mayer-Riemsloh described transmission from father to son, in the family recorded by Best 1 of the parents and 2 of 3 children had the disease (bilateral in both children), in Stallard's case the father had bilateral glioma (one eye was enucleated, in the other eye the tumor underwent spontaneous regression), and he had 2 sons with bilateral glioma. Reiser, in a series of 16 cases of glioma, mentioned 1 in which the mother transmitted glioma to the son. Lange's series of 36 cases included the cases in 2 families with vertical inheritance of glioma. In the first family the father, with glioma in the left eye, had 2 children with bilateral glioma (the case is identical with that presented by Clausen), in Lange's second family the father, who had unilateral glioma, had a child with bilateral glioma. In the family reported by Weller the father lost his eye on account of glioma and had 2 daughters with glioma (1 with bilateral and the other with unilateral involvement). This family is remarkable because the history revealed that the father's father and the great-grandfather had had one eye removed in childhood. Assuming that these eyes were all enucleated for glioma, the tumor occurred in four successive generations of the same family. Benedict and Parkhill reported 4 cases, a case occurring in each of two successive generations of 2 families. In the first family the mother had unilateral glioma and gave birth to a girl with bilateral glioma. In the second family identical twins were involved, 1 of them died of cerebral extension of unilateral glioma (there was no evidence of glioma of the other eye at the time of death), and the second of the pair had involvement of both eyes, this twin had 2 children 1 of whom had bilateral glioma.

Badtke⁹ reported 8 cases in which there was no familial heredity and 2 cases in which there was direct inheritance (from the mother to the second son), Fleischer reported the occurrence of glioma in three generations. Griffith and Sorsby extended the observations of Letchworth, Griffith and Hine, respectively, on the occurrence of glioma in two generations, by reporting its appearance in the third generation of the same family. In the first generation, a man had had one eye enucleated, and he had been cured of the glioma in his other eye, of his 5 children, the first, a premature girl, died on the eighth day after birth. The 4 sons all had glioma (3 with bilateral and 1 with unilateral involvement). The oldest brother (who had been cured of bilateral glioma) had 2 daughters. The first died at the age of 5 weeks, of congenital heart disease, the second had both eyes enucleated because of glioma. If one considers the recent reports, the cases of vertical transmission seem to have increased since attention has been directed to it, as Leber, in 1916, could note only 3 instances (de Gouvêa, Owen, von Hoffmann) of direct transmission, or the more exact knowledge of the disease and early enucleation have resulted in the rescue of more children from death due to the glioma, these persons then reach the age of reproduction and beget glomatous offspring. It is interesting to note that the family trees of patients with glioma are usually free from other hereditary anomalies, with the exception of the family recorded by Badtke, who noted carcinoma, hydrophthalmos, feeble-mindedness, insanity, cirrhosis of the liver and myopia in 6 members of the family afflicted with glioma.

In the recorded cases and in cases already enumerated, the vertical transmission through successive generations was effected through parents (male and female) who themselves had the disease. In the older literature the diagnosis was often only clinical, however, in the more recent literature the clinical diagnosis was confirmed by histologic examination. There is evidence of hereditary transmission in families with glioma through parents not manifesting the disease. This group consists of 8 families, in 4 families the male, and in 4 the female, transmitted the glioma to more than one generation, or it was transmitted through collateral lines. The oldest observation has already been mentioned, that by von Graefe in which several siblings of the mother of another child (with glioma) died in the first year of life of cancer of the eye. Thompson and Knapp and Thompson, respectively

⁹ Badtke, G. Zur Erblchkeitsfrage beim Glioma retinae. *Klin Monatsbl f Augenh* 105 451, 1940

reported on a family in which parents who were free from glioma had a son and a daughter with glioma and a cousin of the father died of glioma. The history showed, also, that the father's aunt lost 2 children because of glioma. Thompson, following the same family for twenty-four years, reported that of the 14 children 5 (2 boys and 3 girls) died of glioma, and the father's great-aunt was reported to have had 3 children who died of cancer of the eye. Steinhilber reported on a family with 10 children, 3 of whom had unilateral glioma. The firstborn, a son who was free from glioma, had 2 children, a boy and a girl, each of whom had the left eye enucleated for glioma. Lukens reported the case of a child with bilateral glioma whose cousin on the father's side had died previously of the disease, and the uncle and aunt recognized the appearance of the eye as similar to that of their child. Owen's publication shows a family in which the grandfather's left eye was enucleated by Bowman, his son had unilateral glioma, and the normal daughter had 8 children, 4 of whom had glioma (3 with bilateral and 1 with unilateral involvement). Berrisford reported on the same family, Owen's description makes the mother of the 8 children not the daughter but the sister, of the grandfather. Waardenburg cited Hemmes, namely, that 4 of 7 siblings of the father had glioma, and, although he did not himself have the disease, 4 out of his 5 children were afflicted. Purtscher recorded a family of 11 children, of whom 2 boys died of bilateral glioma, a normal sister had a son who died of glioma of the left eye. In addition, another sister, unmarried, had abnormalities of both eyegrounds, more pronounced in the left eye, which was nearly blind. The original diagnosis was choroiditis or neoplasm, but repeated examinations led to the opinion of spontaneous retrogression of glioma, which apparently occurs more frequently than it is given credit for. Sabugín's 14 cases include those of 2 brothers with glioma duplex, the mother's brother also had retinal glioma, of which he died. One of the most interesting cases falling into this group is that of Townsend, mentioned before, in which the mother, who did not manifest the disease, transmitted glioma to 3 daughters through 2 husbands (one by the first and 2 by the second marriage).

The collected data from the literature are cited in order to demonstrate the horizontal, vertical and collateral hereditance of glioma. In order to determine the role of heredity in a disease it is necessary to study all members of a family through several generations with respect to the presence or absence of the disease. The study

of the family tree in man is rather limited through such factors as chance matings, the small number of children and the long life span of generations. The determination of the exact part played by heredity in the production of any character becomes one of the most difficult of problems, hence, observations on identical human twins are of paramount importance. Identical twins derive from the same fertilized ovum and necessarily have the same genetic composition, they are either exact duplicates or mirror images of each other. Any disease or anomaly which develops similarly in the two members of the pair is conditioned by the genetic composition of the chromosomes. The research on twins with respect to tumor has revealed information of tremendous importance. McFarland, with Meade,¹⁰ collected from the literature the largest number of neoplasms in identical twins—40 tumors (benign and malignant) occurring in 20 pairs of monozygotic twins. Their report included the family described by Silcock,¹¹ which, similarly, was included in the later compilation of Macklin. The data supplied by Silcock do not warrant the inclusion of his case in the group of tumors of the eye in twins, daughter and mother had melanotic sarcoma of the left eye, with an interval of twenty years. The sister of the mother died of multiple tumor at the age of 40 and lost one eye. A twin sister of this patient, and also her father, lost one eye, but "there was great doubt as to whether in the last 3 cases the loss was due to neoplastic growth." Macklin¹² collected from the literature the cases of 53 pairs of monozygotic and 35 pairs of dizygotic twins with tumor and found that tumor affects both members of a pair of identical twins more frequently than it does both members of a pair of fraternal twins, the age of onset of the tumors shows a similar relation. Of the identical twins, both members were affected by the same type of tumor in the same organ at the same age in 64 per cent, whereas in 36 per cent the other of the pair remained unaffected, of the fraternal twins, both members of the pair were afflicted in 33 per cent, which is about one-half the value for the identical twins. Of the identical twins, the tumor affected the same organ in 93 per cent, of the fraternal twins, in only 58 per cent, even

10 McFarland, J. Problem of Cancer in Twins, *Bull. Am. Soc. Control Cancer* 25:40, 1943.

11 Silcock, A. A. Hereditary Sarcoma of Eyeball in Three Generations, *Brit. M. J.* 1:1079, 1892.

12 Macklin, M. T. Symposium of Gynecologic Cancer, *West. J. Surg.* 50:439, 1942, An Analysis of Tumors in Monozygous and Dizygous Twins, *J. Hered.* 31:277, 1940.

if they belonged to the same sex. Conversely, Charache¹³ presented histories of 3 pairs of homologous twins of which 1 member of each pair was affected, 1 member of 2 pairs having Hodgkin's disease and 1 member of the other pair having osteogenic sarcoma. The 3 affected twins died, and the homologous living members of these pairs had been free of any symptoms for four years and two months, five and one-half years and eight years, respectively, since recognition of the disease in the deceased twin. The basis of identity in twins, the single ovum with division into two blastomeres, each receiving an equal share of genetic influences, material and defects, sheds important light on retinal glioma in identical twins. The material necessarily is scant, and it is surprising to find three papers on the subject. Benedict¹⁴ and Benedict and Parkhill⁵ observed glioma in identical twin girls at the age of about 4 years, 1 of the pair had bilateral glioma and the other unilateral glioma (the same family was mentioned in the group of vertical inheritance). Duncan and Maynard¹⁵ described neuroepithelioma in identical twin sisters at the age of 7 months. In both twins the tumor showed well formed rosettes and areas of differentiating fibrillar glial tissue, both patients succumbed, but the type of extension of the tumor was different in the 2 patients, the difference probably being influenced by the circumstance that, because of the hydrophthalmos present in the first case, trephination was done, resulting in subsequent spread from the orbital region to the upper superior cervical glands. The member of the pair who was not subjected to operation died of intracranial extension of the tumor. Moore's¹⁶ case was that of a girl aged 2 years with bilateral glioma, whose twin sister was free of the disease. Unfortunately, no mention is made of whether the twins were identical or fraternal, and therefore the case adds nothing of value to clinical research. The occurrence of retinal glioma in identical twins raises the question of glioma located in parts other than the retina in such twins, surprisingly, data are available on the subject. Joughin¹⁷ reported

synchronously expanding intracranial neoplasms in identical twin sisters aged 32, both of whom had development of glioma within one and a half years of each other and died, the family history had been negative for tumor for three generations. Leavitt¹⁸ observed identical twin boys, the first child died at the age of 6½ and the second at the age of 8 years. At the time of death of the first twin the second had not shown any symptoms of illness. Autopsy on the first patient revealed a large infiltrating glioma arising from the root of the fourth ventricle, the cellular structure was identical with that of the medulloblastoma described by Bailey and Cushing, with neuroblasts and spongioblasts in small number. No autopsy was performed on the second boy, however, the diagnosis of cerebellar tumor was unquestioned, but the exact location and histopathologic features of the growth remained unconfirmed.

The similarity in type of tumors in homologous organs with about the same age of onset in monozygotic twins emphasizes the importance of the role played by heredity. The number of cases is as yet too small to permit conclusive evidence. All cases of glioma in twins (identical and fraternal) should therefore be published in the future in order that the ratio of concordance to discordance of monozygotic and dizygotic twins may be established. Considering the relatively small number of available instances, the gathering of such material may consume considerable time, but the effort will be rewarded by conclusive evidence. Habs and Dietel,¹⁹ similarly, collected material on uterine carcinoma and found 8 cases in identical twins and no cases in fraternal twins (there were only 2 pairs of fraternal twins in the series), they concluded that hereditary predisposition to carcinoma of the uterus seems to be assured but not proved, and they urged the compilation of larger series of cases and longer periods of observation of the still unaffected member of the pair. Lehmann pointed out that the ratio of concordance to discordance differs in identical and in fraternal twins, the percentage of concordance in identical twins being larger, considering the localization and type of the tumor, on the basis of these figures carcinoma of the stomach in the twin material shows a hereditary disposition, but the same is not true of carcinoma of other organs.

13 Charache, H. Tumors in One of Homologous Twins, Hodgkin's Disease, Osteogenic Sarcoma, *Am J Roentgenol* **46** 69, 1941.

14 Benedict, W. L. Retinoblastoma in Homologous Eyes of Identical Twins, *Arch Ophth* **2** 545 (Nov) 1929.

15 Duncan, W. J. L., and Maynard, R. B. M. Bilateral Glioma in Twins, *Tr Ophth Soc Australia* **1**: 125, 1939.

16 Moore, E. Clinical and Pathological Report of Bilateral Glioma Retinae, *Proc Roy Soc Med* **22** 951, 1929.

17 Joughin, J. L. Coincident Tumor of the Brain in Twins, *Arch Neurol & Psychiat* **19** 948 (May) 1928.

18 Leavitt, F. H. Cerebellar Tumors Occurring in Identical Twins, *Arch Neurol & Psychiat* **19**: 617 (April) 1928.

19 Habs, H., and Dietel, H. Zwillingsforschung bei Uterus-Carcinom, *Klin. Wchnschr* **20** 8, 1941.

The glomatous fraternities, the vertical familial distribution appearing in successive generations or in collateral lines and the research on gliomas of the retina and brain in twins are the factual evidence at one's command in the search for hereditary factors. Further evidence in support of the hereditary basis is the possible connection of glioma of the brain in families with glioma of the retina. Regarding this association evidence is almost completely lacking. Marshall and Leber mentioned that in a family with multiple glioma of the retina an unaffected child died suddenly with convulsions, and Vetsch reported 2 families with glioma in which one or two unaffected children died of convulsions or cerebral disease of inflammatory nature. One would have to stretch the imagination to arrive at the diagnosis of glioma of the brain from the scanty reports of these cases. The acceptable case seems to be that of Elschning cited by Leber, that of a 2 year old girl with unilateral glioma whose 13 year old sister ten years later died of infiltrative glioma of the large hemisphere of the brain. The cases to be reported seem to belong in this group of hereditary influences and the uniqueness of the observation therefore warrants the detailed report of the family history.

CASE 1—D W., a boy aged 8 months, had his left eye enucleated. The right eye was treated with roentgen radiation and then enucleated three months later.

The blood group was B. A blood count revealed 8,500 leukocytes, with 35 per cent polymorphonuclear leukocytes, 55 per cent lymphocytes, 11 per cent endothelial leukocytes, 8 per cent eosinophils, 1 per cent stab forms and 48 per cent hemoglobin. Erythrocytes numbered 3,350,000 with marked achromia and anisocytosis and poikilocytosis.

Both enucleated eyes were embedded in paraffin, examination revealed the picture of retinal glioma with formation of true and pseudorosettes, i. e., a neuro-epithelioma. The differences in the two tumors were quantitative, not qualitative. There were the typical features of retinal glioma, namely, the darkly stained nuclei without visible protoplasm, densely packed in perivascular bands or cuffs. Between the cuffs of living cells were large masses of poorly stained necrotic cells, with hardly visible contours and small foci of calcification. In the left eye the tumor filled the vitreous cavity, in the right eye the tumor cells originated apparently in the layer of ganglion cells and in the inner nuclear layer and invaded the other layers of the retina and, in the posterior part of the globe, the choroid also. In the right eye the infiltration was of such degree that the normal retinal structure could hardly be ascertained. The cells were of the usual small round cell type, with almost no cytoplasm, the hyperchromatic nuclei were spherical, polygonal or wedge shaped. A small number of typical rosettes were distinguishable, a small radially arranged group of cells surrounding the central lumen. The lumen was circular in all sections, the groups of cells therefore representing small hollow spheres. The lumen was marked by a delicate refractile limiting membrane. Pseudorosettes were more numerous, the cells were

arranged in short arcs or complete circles about clear spaces which were filled with fibrillar material. The optic nerves were not involved.

The left eye was enucleated at the age of 8 months. The right eye was treated with roentgen radiation, not only did the treatment fail to stop the growth, but the rapid progression of the tumor necessitated the removal of the second eye at the age of 11 months.

The mother of the child and the mother of the child in the next case were sisters. The family histories were entirely negative for glioma and for all other forms of malignant growth. Each child was the first and only child of the mother.

CASE 2—M J C., a girl aged 5 years, was admitted to the hospital with the complaint of vomiting, which according to the mother was of projectile type. Since the vomiting had started, about one month before, the child had lost 3 pounds (1.3 Kg.) in weight. For one week before admission, the mother stated, the child had been vomiting everything she had eaten.

Physical examination revealed a blood pressure of 120 systolic and 80 diastolic. The child was well developed but thin, she appeared chronically ill but showed no evidence of dehydration. There was bilateral cervical adenopathy of slight degree. Tachycardia was present, with a pulse rate of 120 per minute. Examination of the thorax, abdomen, head and eyes revealed nothing abnormal. The Babinski sign was present bilaterally, Kernig's sign was absent.

The urine was normal. Studies of the blood revealed a hemoglobin content of 91 per cent, a red cell count of 4,700,000 and a white cell count of 5,800 per cubic millimeter, with 48 per cent polymorphonuclear leukocytes and 54 per cent normocytes and normochromic cells, a negative Widal reaction for typhoid and paratyphoid, a negative reaction for undulant fever, and a protein content of 19 Gm. per hundred cubic centimeters. A flat plate of the abdomen, after a barium sulfate enema, and a roentgenogram of the chest showed a normal condition. The Mantoux test gave a negative reaction to tuberculin in a dilution of 1:10,000, and the reaction to a dilution of 1:1,000 was negative after forty-eight hours.

Increased intracranial pressure was suspected and a suboccipital decompression, with postoperative roentgenologic treatment, was performed. The child failed to improve. She did not talk, she ate well but vomited. She moved the left arm and leg only occasionally. The head, eyes, neck and lungs were normal. Tachycardia was noted. The right leg was spastic, the toes were extended and inverted at the ankle joint, and the right arm was spastic and rotated inward, with wrist drop. The abdominal reflexes were absent, the Babinski sign was present bilaterally, there was a knee clonus on the right, and the ankle jerks were absent.

On consultation with another brain surgeon, the diagnosis of left-sided subdural hematoma was persistently suggested, despite observations at the previous operation. For that reason a burr hole was made in the left frontal region. The dura was tense and did not pulsate. When the dura was opened a tense brain was exposed, without any evidence of subdural hematoma. A brain cannula was inserted, striking a dilated ventricle and approximately 60 cc. of air was injected after a similar amount of ventricular fluid was removed in divided amounts.

Closure was carried out in the usual manner. Ventriculographic study showed a symmetric dilatation of the ventricular system up to the aqueduct, which was not visualized, a state presumably indicative of an expanding lesion of the brain stem. The condition

after the operation became progressively worse, and the child died thirty-six days after the second operation, or about four months after the initial symptoms were established

Observations at Autopsy—The body was that of an emaciated, 5 year old white girl in complete rigor mortis. The skin was pale, dusky and dry. No petechiae or jaundice was noted.

Head The hair of the forehead was cut short, the hair over the back of the head had been shaved, and

The meninges were delicate, the gyri were flattened, and the sulci were narrowed and compressed. The brain appeared large. The pons and the brain stem anterior to it were the site of a whitish, club-shaped tumor, measuring 8 by 4 by 3 cm. The floor of the third ventricle had herniated and was thinned. When the corpus callosum was cut, an increased amount of clear cerebral fluid escaped. All the ventricles were greatly distended. The cerebral vessels did not appear unusual.

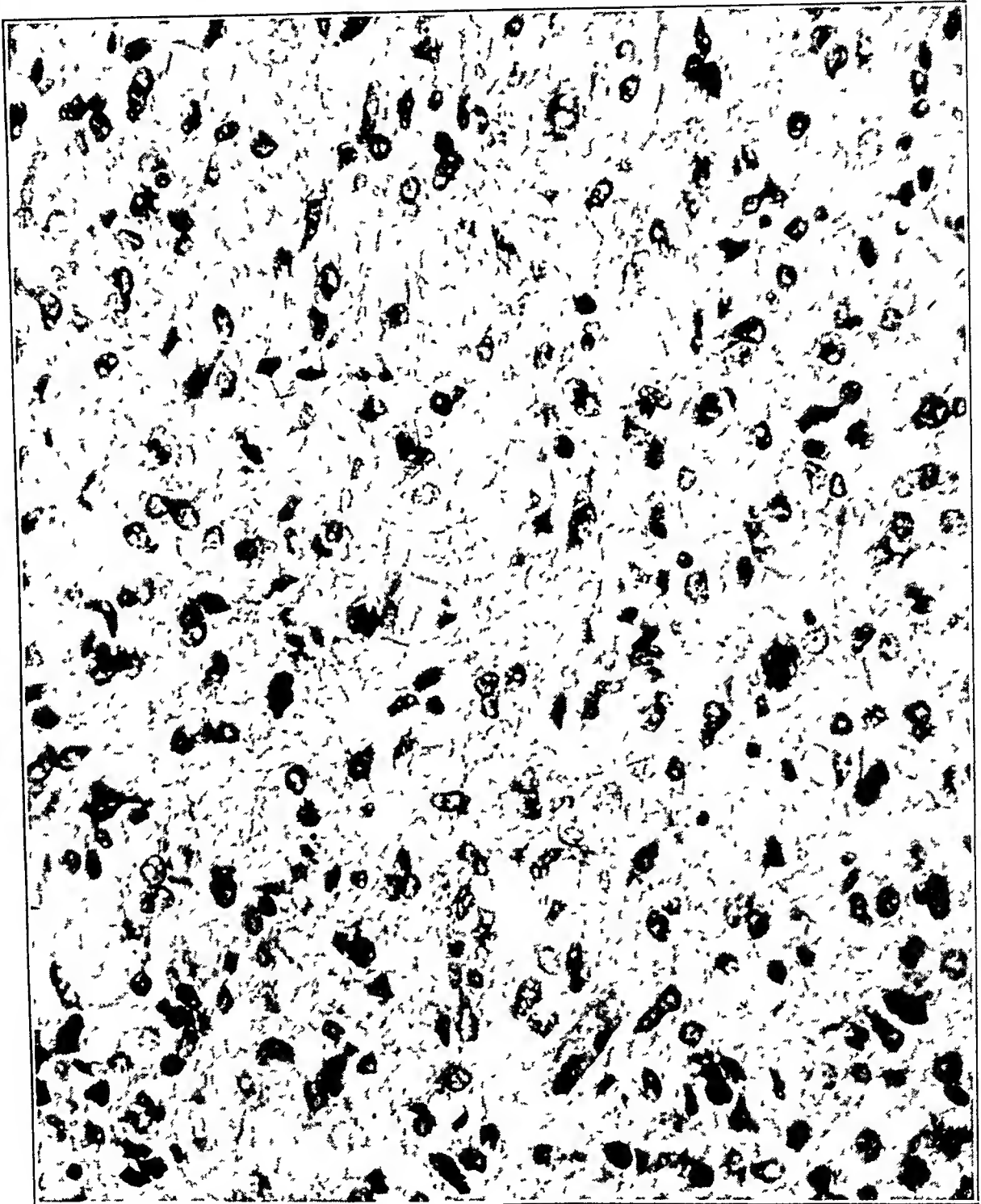


Fig 1—Section from the part of the brain tumor, exhibiting a fibrous stroma. Cell with round and oval nuclei and the interlacing character of the processes are clearly visible. Magnification, $\times 465$

here a semicircular, healed scar was noted. The head was large, the galea was not unusual. The bones of the calvaria were thin and translucent. Portions of both occipital bones were absent, having been removed at a previous operation. Also noted was a trephine opening in the lateral aspect of each parietal bone. When the skull was opened, the dura was found to be tense. The sinuses contained liquid blood, no thrombi were noted.

Chest The thymus was small. Both pleural spaces were free of fluid and adhesions.

The heart lay free in the pericardial sac, which contained a small amount of clear, yellowish fluid. The epicardial surface was smooth and glistening. The endocardium was thin and smooth throughout. All the valves were thin and delicate. In the outflow tract of the left ventricle a subendocardial hemorrhage was

noted The myocardium was reddish and of firm, muscular consistency A few atheromatous plaques were noted in the ascending portion of the aorta, near the aortic valve No developmental defects were noted

Lungs The lungs were fluffy and of cushion-like consistency The pleura was smooth and grayish On section, the parenchyma was noted to be aerated throughout and reddish The bronchi and the pulmonary vessels were not unusual

was paper thin and bulged outward A notching due to herniation through the incisura was seen The aqueduct and the third and lateral ventricles showed considerable dilatation

On section, the pons and the mesencephalon appeared swollen, owing to the infiltration of tumor, which was cystic and filled with greenish, soft, gelatinous material, the cyst was irregular in shape and had irregular peripheral extensions, it measured approximately 3 cm in



Fig 2—High power magnification ($\times 870$) of same part of the tumor as that shown in figure 1

Abdomen The abdomen was scaphoid The subcutaneous fat tissue appeared wasted On section, drops of clear fluid escaped from the cut surface The peritoneal cavity was free of fluid and adhesions The organs were normal in color, size and relation to each other, no gross changes were noted No developmental defects were present

Brain There was deep grooving by the basilar artery The tumor had caused "hypertrophy of the pons" and grew forward into the peduncles, which were of twice the normal size The floor of the hypothalamus

diameter in some areas The tissue about it was semi-firm and grayish white and showed streaky brown hemorrhages and greenish gray mottling The appearance was that of glioblastoma multiforme The fourth ventricle was pushed upward and to the left and was almost completely occluded in one area

Diagnosis—The diagnosis was pontile tumor producing obstruction of the sylvian canal and the fourth ventricle, with internal hydrocephalus

The status was that usually observed five weeks after trephination

Microscopic Examination of the Tumor (Dr M Tarlow)—The tumor was moderately cellular and presented cysts of variable size. The cells were fairly uniform in appearance and contained round or oval nuclei, in which there was chromatin of moderate amount. Nucleoli were absent. The rather fibrous stroma was composed of interlacing processes of the cells, which contained moderate amounts of cytoplasm. Even in preparations stained with hematoxylin and eosin the type cell was clearly revealed as the astrocyte. In some regions there was a tendency toward clumping of nuclei, and few true multinucleated cells were present. Mitotic figures did not occur. The margins of the tissue presented a few very large, well formed cells with abundant granule-containing cytoplasm and nuclei with nucleoli. These cells doubtless represented inclusion nerve cells. Areas of necrosis in which fantom cell forms were seen occurred in association with cysts. The walls of the cyst were formed of glia cells, frequently clearly visible as flattened astrocytes. A considerable number of rather thin-walled blood vessels was seen in certain portions of the cyst wall.

The tumor presented the characteristic features of a fibrous astrocytoma in which cyst formation had occurred.

COMMENT

The familial tendency of retinal glioma is well established. In the present cases pure coincidence certainly would not be sufficient to explain the occurrence of glioma duplex of the same histologic type, that of neuroepithelioma in 1 and of astrocytoma of the brain in the other, in children whose mothers were sisters. The occurrence of malignant growths of the same type in the retina and in the brain in collateral lines is presented for the first time, here, the females, themselves not affected, were the transmitters to a male (first case) and to a female (second case) child, respectively. Such observations are necessarily rare, for they usually escape attention. Even in these cases clinical observation and operative intervention failed to disclose the true picture, and only autopsy furnished the proper and indisputable evidence of the neoplasm of the brain. Without the permission for autopsy in the second case the bilateral glioma in the first child would necessarily be recorded as of sporadic occurrence.

The influence of heredity in mammary tumors of mice is one of the most widely studied subjects in connection with heredity and cancer in general. Inbred strains of mice of brother and sister matings have been under observation for more than fifty generations. Bittner²⁰ found that three influences, or inciters, in the occurrence of spontaneous tumors of the breast in

mice are present, (a) the milk influence (extra-chromosomal), transmitted by nursing; (b) hormonal stimulation, dependent on intrinsic or extrinsic factors, and (c) inherited susceptibility, which may be transmitted by males or females. The importance of the research cannot be overemphasized, but the work is hardly applicable to human cancer, which is seldom obviously hereditary. Broca, Wartkin and others reported on families with such a high incidence of cancer that it could hardly be attributed to chance alone. Roberts and Roberts reported the concurrent development of osteogenic sarcoma in 1 brother and 2 sisters, and Miltzer²¹ described simultaneously developing carcinoma in the same part of the stomach in identical twins 70 years of age. Hereditary susceptibility to cancer seems to become intensified in families in which the parents have the same type of cancer. Bauer's concept of a predisposition of certain organs to cancer was opposed by Ewing²² and others, who stated the belief that either inherited susceptibility to cancer is negligible or there does not exist any specific hereditary predisposition in human cancer. It must be borne in mind, also, that cancer is not a disease entity and that even the establishment of a hereditary factor in one form of cancer would not permit generalization for all forms of cancer. According to Crabtree,²³ the incidence of fatal cancer in parents and siblings of white females with cancer of the skin is nearly twice the expectation on the basis of normal experience. For patients with cancer of the breast or cervix the familial incidence is more than one and a half times the normal expectancy. For males with cancer of the skin there is excessive familial incidence only in the cases in which the carcinoma develops at a relatively early age. The excessive familial incidence does not necessarily imply genetic factors, as cancer of the skin may be the result of environmental factors, cancers of the breast and cervix are more probably representative of hereditary origin. Waaler, in Norway, based his conclusion on 6,000 cases of carcinoma in which there appeared to be a hereditary predisposition of certain organs for malignant growths. Habs and Dietel cited an incidence of 8 per cent for carcinoma of the uterus in the twins of patients who were free of the tumor at death and of 34 per cent in the sisters of the afflicted.

20 Bittner, J. J. Observations on Genetics of Susceptibility for Development of Mammary Cancer in Mice, *Cancer Research* 2:540, 1942, Possible Relationship of Estrogenic Hormones, Genetic Susceptibility and Milk Influence in Production of Mammary Cancer in Mice, *ibid* 2:710, 1942.

21 Miltzer, R. E. Carcinoma of the Stomach in Identical Twins, *Am J Cancer* 25:544, 1940.

22 Ewing, J. Heredity and Cancer, *Bull Am Soc Control Cancer* 24:4, 1942.

23 Crabtree, J. A. Observations on the Familial Incidence of Cancer, *Am J Pub Health* 31:49, 1941.

patients, for carcinoma of the breast the figures were 16.5 and 44.7 per cent, respectively. Wood and Darling²⁴ presented the record of a family with frequent occurrence of bilateral carcinoma of the breast in four generations, an exception was a woman in the second generation, in whom the carcinoma developed in the cervix. The predisposition was transmitted through the maternal line of descent. Attention was drawn to this family during the study of the third generation, consisting of 3 sisters, all of whom had bilateral cancer of the breast. In 1 female of the fourth generation cancer of the breast developed at the age of 18. Cancer of the breast occurred only in those women who had been nursed by their mothers, a factor possibly analogous to the milk inciter of Bittner in mammary carcinomas in mice. There was no inbreeding in the family, and in the main line of descent only 1 of the fathers had carcinoma, in his case, of the colon, therefore a monohybrid recessive factor existed, causing semidominant inheritance within the family. A family with 5 sisters with mammary carcinoma, in 3 of whom the disease was bilateral, was reported by Handley. The observations of Bergen, Mayo and Giffin²⁵ included a study of 176 patients with proved cancer of the large intestine, in whose families the incidence of cancer was high. Forty-two per cent of the relatives had gastrointestinal cancer, as compared with 27 per cent of the two control groups. In their opinion, Bauer's concept of organ susceptibility is reasonable and warranted, as the offspring of persons with intestinal cancer had more often malignant growths of the intestinal tract than children both of whose parents were free of the disease. Conversely, Hanhart²⁶ could not determine a similar predisposition in his material, based on the study of descendants of 121 married couples, both of whom had cancer. Both partners of 33 of the 121 married couples had cancer of the stomach, and only 11 per cent of their children had a similar condition. Of the 121 couples, only 30 had children in whom cancer developed. A total of 590 children sprang of these marriages, the average expectancy of cancer for 286 of these offspring when past 50 years of

age amounted to about 13 per cent, as compared with an expectancy of about 20 per cent for the population in general. Hanhart's study gave results much like those of investigations on twins, namely, the absence of a specific hereditary predisposition to cancer.

The scantiness of hereditary influences in human cancer is obvious when one considers the enormously high incidence of the ailment. Susceptibility to a certain degree may be transmitted by cancer of the breast from mother to daughter, but carcinoma of the prostate in the father does not predispose his daughter to any form of cancer. Human cancer is seldom obviously hereditary, like hemophilia, brachydactyly, polydactyly and color blindness. On the other hand, glioma and neurofibromatosis, within the group of malignant growths, are strikingly hereditary and therefore represent a distinct class in themselves.

The relatively large number of sporadic cases of glioma without familial tendency constituted a point of controversy in establishment of the hereditary character of glioma. To the known cases of sporadic occurrence McCrea²⁷ recently added 12 (3 of bilateral and 9 of unilateral glioma), and I am adding 8 cases of unilateral and 1 case of bilateral glioma. This frequency of the sporadic form has led some authors to postulate a familial and a sporadic type of retinoblastoma, the latter the expression of somatic mutation. According to Best, the somatic mutation becomes hereditary, with a greater degree of penetration than in the previous generation. Weller emphasized that the person with retinoblastoma representing an apparent somatic mutation may become the originator of familial retinoblastoma if he survives and marries. One cannot fail to see the correctness of this assumption and may go even further and point out that the limited number of children of the present day urban population, together with the fact that many parents who have produced gliomatous offspring will refuse to have more children, or will refuse permission for enucleation of the second eye of a bilaterally affected child, helps to make the picture more obscure. Through the refusal to have more children or through the small number of children an apparent sporadic appearance obscures the possible existence of gliomatous fraternities, through refusal of permission for enucleation of the second eye the life of the affected child falls short of the age of reproduction, and therefore the patient with apparent sporadic

24 Wood, D. A., and Darling, H. H. Cancer Family Manifesting Multiple Occurrences of Bilateral Carcinoma of Breast, *Cancer Research* **3** 509, 1943.

25 Bergen, J. A., Mayo, C. W., and Giffin, L. A. Familial Trends in Human Cancer, *J. Hered.* **31** 511, 1940.

26 Hanhart, E. Auffallend geringe Bedeutung der "Belastung mit Krebs" bewiesen durch das sehr häufige Freibleiben der Nachkommen aus 121 Ehen krebserkrankter Gatten im Kanton Glarus, Schweiz. *med. Wchnschr.* **73** 446, 1943.

27 McCrea, W. B. E. Glioma of the Retina. A Review of Twelve Cases, *Brit. J. Ophth.* **27** 259, 1943.

glioma does not become the founder of a family with vertical inheritance of the condition. Lenz pointed out that sporadic occurrence is the rule in the recessive type of inheritance and that the number of sporadic cases is necessarily greater with a small number of children. The tendency to inheritance of glioma apparently may be both dominant and recessive. In dominant inheritance the disease appears in the children when only one parent carries the trait, and usually about 50 per cent of the offspring are affected. In recessive inheritance, except for the sex-linked variety, both parents must carry the trait if the disease is to appear in any of their children, hence, the large number of cases of consanguinity associated with recessive inheritance. Most of the severe diseases are recessive and the mild ones dominant. The large number of glomatous children within a fraternity and the apparent direct transmission through mother or father speak eloquently for a dominant single hereditary factor. The cases in which glioma is present in more than one generation with normal parents suggest a recessive mode of inheritance. According to Waardenburg,²⁸ consanguinity is often present in cases of glioma, which is contradictory to the observation of most authors, who have pointed out that the absence of consanguinity is evidence against the recessive mode of inheritance. The ratio of normal to affected children in most of the families indicates dominance, according to the figures of Franceschetti,²⁹ who found the ratio 63/77 for 25 families. Passow³⁰ expressed the belief that glioma shows a dominant or a recessive heredity. Clausen expressed doubt that dominant and recessive factors were present, he stated that glioma depends on one factor and is inherited through direct or indirect transmission and that some promoting or releasing factor, in addition to other elements, is essential. Hemmes concluded that not all the parents, children and siblings of his patients would be free from glioma if the disease were dominant, but, simultaneously, he ventured an opinion that the relatively rare incidence of consanguinity (in 3 of his 48 cases) spoke against the recessive mode. Nine patients with healed glioma of unilateral type were more than

25 years of age, 4 of them the parents of 9 healthy children. The 48 patients had 211 siblings over the age of 5 years, all of whom were free from glioma. The collateral lines were free, 24 patients with glioma had 76 siblings, who were parents of 281 unaffected children. Waardenburg concluded that both dominant and recessive inheritance is evident and that the cases of unilateral glioma suggest mediation of some disturbing influence in the hereditary mechanism, not hereditary somatic mutation. According to Aschoff and others, hereditary cytokinetic or somatokinetic disturbance plays a part. Badtke commented in connection with the mode of inheritance that the phenotypically normal are not necessarily genotypically normal and that only the careful watching of the offspring through many generations can furnish the answer. Best stated that mendelian laws do not apply to glioma and assumed that an unknown, but hereditarily established, derangement is present.

Griffith and Sorsby suggested that hereditary glioma represents a distinct histologic entity which differs from the sporadic variety, the exciting or inhibitory factors not necessarily being genetic, since environmental as well as genetic factors may suppress or make manifest the given genetic tendency. According to their opinion, glomatous fraternities with unaffected antecedents are suggestive of recessive inheritance, but the incidence of 47.8 per cent, as against the theoretic incidence of 25 per cent, together with the absence of consanguinity, speaks against the recessiveness of the trait. Glioma in direct transmission was evident in 28 pedigrees (an incidence of 61.1 per cent in 19 available complete sibships). Genetic analyses show dominance, though irregular in type, as gliomas occurred in children of parents of an affected stock who were themselves unaffected.

The available data furnish no clearcut evidence that the factor or factors determining the heredity of glioma behave as does either a simple mendelian dominant or recessive trait. This confused picture suggests that a possible somatic variation, probably a structural anomaly of the retina, is inherited and that on this basis retinoblastoma may or may not develop. The hereditarily determined somatic variation, according to Weller, is capable of varying degrees of intensity. Simple mendelian recessive defects of the retina are known to occur in the mouse (Keeler) and the rat (Bourne, Campbell and Tausley), furthermore, Weller cited the occurrence with glioma of coloboma of the iris (Wintersteiner) and of small malformations, even very small tumors (Fuchs), and the obser-

28 Waardenburg, P. J. *Das menschliche Auge und seine Erbanlagen*, Haag, M. Nijhoff, 1932.

29 Franceschetti, A. *Die Vererbung von Augenleiden*, in Schieck, F., and Bruckner, A. *Kurzes Handbuch der Ophthalmologie*, Berlin, Julius Springer, 1930, vol. 1, p. 476.

30 Passow, A. *Hereditäre Augenerkrankungen, das Glom der Netzhaut*, in Bumke, O., and Foerster, O. *Handbuch der Neurologie*, Berlin, Julius Springer, 1936, vol. 16, p. 934.

vation of Ch'in concerning the overlapping of malformation and neoplasm as examples of presumptive preblastomatoid lesions. The changes in the opposite eye, the retrogression of glioma, suggest such structural deviations, as do the changes in neurofibromatosis and tuberous sclerosis, which represent developmental lesions rather than true neoplasms. Retinoblastoma apparently belongs to the same group, conditions which have a hereditary basis and originate from lesions intermediate between developmental disturbances and true neoplasms.

SUMMARY

The hereditary basis of malignant growths, especially that of retinoblastoma, is evaluated with reference to horizontal, vertical and collateral inheritance in the family history, and the importance of research on twins is stressed.

A case of glioma of the retina and 1 of glioma of the brain occurring in collateral lines, hitherto undescribed, are reported.

31 Lincoln Park

INJECTION OF OXYGEN INTO TENON'S CAPSULE

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AND

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Injection of contrast mediums into Tenon's capsule, as described by Spackman,¹ has proved invaluable in the localization of intraocular foreign bodies. This is especially true of the type of injury incurred in jungle warfare, in which hand grenades, booby traps and small antipersonnel mines are used extensively. These usually cause multiple, small, penetrating wounds, containing opaque foreign bodies of varying sizes, which roentgenographically look like "snow flurry" collections of opaque debris. When the region of the eye is involved, it is frequently impossible to distinguish intraocular foreign bodies from those outside the eyeball by any procedure except roentgenographic study with injection of a contrast medium into Tenon's capsule (fig 1). This method is also of consid-

erable was diagnostic and enabled one to localize intraocular foreign bodies, it made hazardous any surgical intervention soon after the injection. This was especially true when the anterior chamber had to be opened, as for the removal of a foreign body by the anterior route or for linear extraction of a traumatic cataract or, at times, for the simultaneous performance of these two procedures. The air in Tenon's capsule exerted external pressure on the eye-

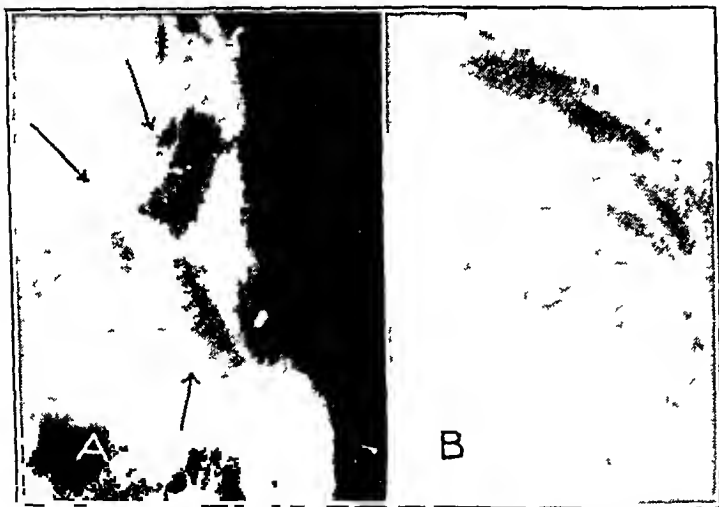


Fig 1—Multiple intraocular mortar fragments localized by air studies of Tenon's capsule

able assistance in the localization of foreign bodies lying near the limits of the globe and in diagnosing double perforations of the eyeball.

Early in our experience injections of air were made into Tenon's capsule. About 6 cc was injected into the capsule, after which stereoscopic roentgenograms were obtained without the Bucky diaphragm in the posteroanterior and lateral projections (fig 1). While the pro-

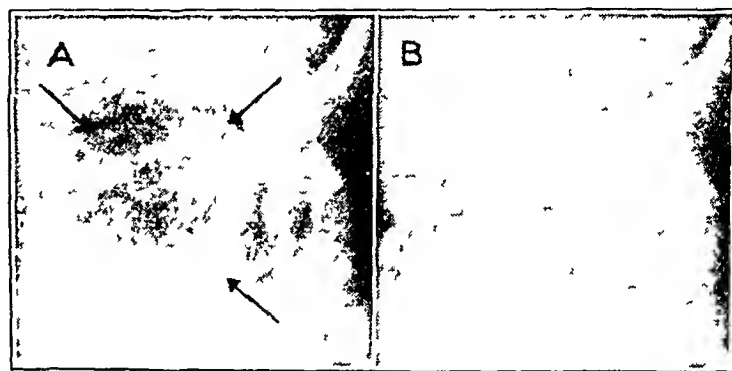


Fig 2—Injection of oxygen into Tenon's capsule. A, roentgenogram made immediately after injection, B, roentgenogram four hours after injection, revealing considerable absorption of oxygen.

cedure was diagnostic and enabled one to localize intraocular foreign bodies, it made hazardous any surgical intervention soon after the injection. This was especially true when the anterior chamber had to be opened, as for the removal of a foreign body by the anterior route or for linear extraction of a traumatic cataract or, at times, for the simultaneous performance of these two procedures. The air in Tenon's capsule exerted external pressure on the eyeball, increasing the incidence of loss of vitreous and prolapse of the iris. Because of this, carbon dioxide and then oxygen, both known to be absorbed more rapidly than air from tissues or closed spaces, were tried in an effort to minimize the dangers of increased extraocular pressure at operation.

In our experience, air injected into Tenon's capsule was not absorbed completely for three to four days. Most of the air could still be seen at the end of twenty-four hours, disappearing slowly thereafter. Carbon dioxide, on the other hand, was absorbed too rapidly to be effective as a contrast medium. Decreasing amounts of the gas were noted between the first and the last exposure of a routine roentgenographic study. When, for technical reasons, the examination had to be repeated, there was barely enough carbon dioxide in Tenon's capsule to outline the globe.

1 Spackman, E. W. X-Ray Diagnosis of Double Perforation of Eyeball After Injection of Air into Space of Tenon, *Am J Ophth* 15 1007-1012 (Nov) 1932

Oxygen proved to be an ideal gaseous agent. It produced excellent visualization of the globe and was absorbed slowly enough to permit reexamination when necessary, yet the oxygen was absorbed fast enough to avoid the risk of vitreous escaping at operation. Most of the oxygen was absorbed within four to eight hours though a slight amount could still be visualized twenty-four hours after the injection (fig 2).

The technic described by Spackman¹ for injecting air into Tenon's capsule was used (fig 3). A curved no. 25 needle attached to

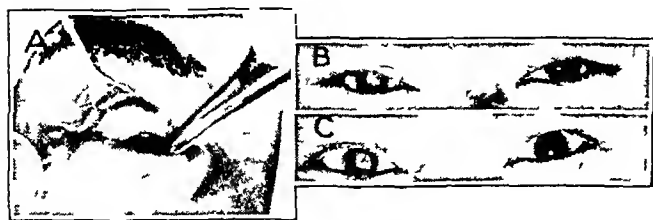


Fig 3—Injection of oxygen into Tenon's capsule. *A*, manner in which the eye is fixed and the needle is inserted; *B*, appearance of the eye before injection; *C*, appearance of the eye immediately after injection of 6 cc of oxygen. Note the cataract in the injured eye.

a 10 cc syringe was employed. The eye was turned downward and inward by a fixation forceps and the needle inserted approximately 5 to 6 mm behind the limbus, the point proceeding subconjunctivally for a few millimeters in the upper outer quadrant of the eye, before entering Tenon's capsule. The oxygen was

introduced slowly and in successful injection immediately produced proptosis. Approximately 6 cc of oxygen produced adequate visualization.

The oxygen was obtained from an ordinary oxygen tank with a sterile rubber tube which contained a cotton filter. The oxygen was allowed to flow through the tubing for several seconds, after which it was introduced directly into the barrel of the syringe through the point for attachment of the needle, displacing the plunger as it entered the barrel. The needle was then quickly applied and the injection carried out.

Griffin, Gianturco and Goldberg² described a stereoscopic method for localizing intraorbital foreign bodies in which a semiopaque artificial eye was used to outline the globe. We compared this procedure with injections of air into Tenon's capsule to see how often the image of the artificial eye coincided with the contour of a patient's eye delineated with air. The major portion of the artificial eye invariably was superimposed on the patient's eye. Their outer margins, however, usually did not coincide. Enough discrepancy existed to convince us that, in our hands at least, the artificial eye was of limited value in localizing foreign bodies lying within several millimeters of the sclera.

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2 Griffin, E. P., Gianturco, C., and Goldberg, S. A Stereoscopic Method for Localization of Intraorbital Foreign Bodies, *Radiology* 40: 371-374 (April) 1943.

CLINICAL STUDY OF EFFECT OF TOBACCO ON THE NORMAL ANGIOSCOTOMA

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In 1926 the classic form of the angioscotoma was first described¹. This work has been a source of aid to clinicians investigating disease of the nasal accessory sinuses,² forms of edema,³ glaucoma⁴ and menstrual disturbances⁵. The research worker, too, has had recourse to angioscotometry in studying the effects of sulfanilamide,⁶ inhalation of oxygen,⁷ and amphetamine sulfate,⁸ and studies of the effects on the visual fields of high altitude⁹ have been a basis of investigations in World War II. No effort has been made, however, to determine the effect of smoking on the normal angioscotoma. Since tobacco smoking is so widespread, it was thought that knowledge of its effect might be of clinical and experimental value. It was therefore decided to study the effect on the central visual fields of smoking 1 cigaret with inhalation

METHODS AND MATERIAL

Angioscotometry was the method used in plotting the central visual fields. The word "angioscotoma" signifies a "defect of the visual fields resulting from the blind spot of Mariotte and related in form to the pattern of distribution of the retinal vessel tree"¹. The shadows, after extensive research, have been interpreted as arising through modifications in the functions of the retinal perivascular spaces¹⁰ and in the retinal synaptic junctions.

Technic—The scotoma was mapped by the method advocated by Evans¹¹. The defects in the visual fields could thus be studied both qualitatively and quantitatively.

Both the Evans and the Lloyd stereocampimeter and charts were used. Monocular fixation was employed throughout the experiment. The subject was permitted to rest for approximately ten minutes before the actual mapping was begun. He indicated the disappearance of the test object by tapping with a pencil or by saying "gone". The diameters of the test objects used ranged from 0.4 to 0.6 mm. Illumination of the test chart was approximately 15 foot candles. The blindspot of Mariotte was outlined. Then the two main superior angioscotomas were plotted, care being taken at all times to move the test object at right angles to the border of the defect.

Subjects—When this work was begun, a series of 8 subjects were studied merely for the qualitative effect, in order to become familiar with the characteristics of the anticipated changes. When, after study of this series, it became evident from the results obtained that inhalation of tobacco produced an effect on the visual fields, a series of 6 subjects were studied quantitatively, the time, blood pressure and pulse rate being correlated with the changes in the field defect. The ages of the subjects ranged from 17 to 28 years. No subject was chosen unless he or she inhaled while smoking. The extent of the habit in the subjects varied from 3 to 20 cigarettes per day. Each subject had had a physical examination at least six months prior to the time that the test was made and had been found to be in good health.

Procedure—At the time the test was made the subject had not smoked for at least one and one-half hours. He rested for approximately ten minutes before any mapping was begun. During this period the pulse and the blood pressure were recorded. The subject was familiarized with the apparatus and instructed to respond either by tapping with a pencil or by saying "gone".

¹⁰ Evans, J. N. Angioscotometry, *Am J Ophth* 9 489-506 (July) 1926, footnote 1.

¹¹ Evans, J. N. Clinical Scotometry, New Haven, Conn., Yale University Press, 1937.

Read at a meeting of the Brooklyn Ophthalmological Society April 19, 1945

From the Department of Ophthalmology of the Long Island College of Medicine and the Long Island College Hospital

¹ Evans, J. N. A Preliminary Report of the Retinal Vessel Scotoma, *Am J Ophth* 9 118-119 (Feb) 1926

² Evans, J. N. Application of Angioscotometry to the Study of Nasal Accessory Sinus Disease, *Ann d'ocul* 169 717-730 (Sept) 1932

³ Evans, J. N. The Scotometry of Retinal Edema, *Am J Ophth* 16 417-424 (May) 1933

⁴ Evans, J. N. Transient Fluctuations in the Scotoma of Glaucoma, *Am J Ophth* 18 333-347 (April) 1935

⁵ Evans, J. N. A Scotoma Associated with Menstruation, *Am J Ophth* 24 507-519 (May) 1941

⁶ Rosenthal, C. M. Changes in Angioscotomas Associated with the Administration of Sulphanilamide, *Arch Ophth* 22 73-81 (July) 1939

⁷ Rosenthal, C. M. Changes in Angioscotomas Associated with the Inhalation of Oxygen, *Arch Ophth* 22 385-392 (Sept) 1939

⁸ Rosenthal, C. M., and Seitz, C. P. Alterations in Angioscotomas Following the Oral Administration of Benzedrine Sulphate, *Am J Ophth* 23 545-549 (May) 1940

⁹ Evans, J. N., and McFarland, R. A. Effects of Oxygen Deprivation on Visual Fields, *Am J Ophth* 21 968-980 (Sept) 1938

The first map, or control, was then plotted. The subject was then given a popular brand of cigaret (one brand being used exclusively), and 40 mm of it was smoked. He inhaled as frequently as was his habit at other times. A second chart was plotted immediately after the smoking, and the pulse and blood pressure were recorded. The same technic was employed at fifteen to twenty minute intervals until the control stage was again reached.

RESULTS

The accompanying charts and tables illustrate the results obtained. They show clearly that inhalation of 1 cigaret increased the area of the

seventeen to forty minutes after the last inhalation. The average time was twenty-four minutes. In sixty to one hundred and seven minutes the effect was completely gone. The average time was seventy-eight minutes.

The effect on the blood pressure did not vary more than 2 to 5 mm of mercury. Whereas the changes in blood pressure were negligible for all subjects, the pulse rate increased as much as 20 beats per minute in 1 subject. The greatest increase in the pulse rate corresponded in time to the most pronounced changes in the angiosco-

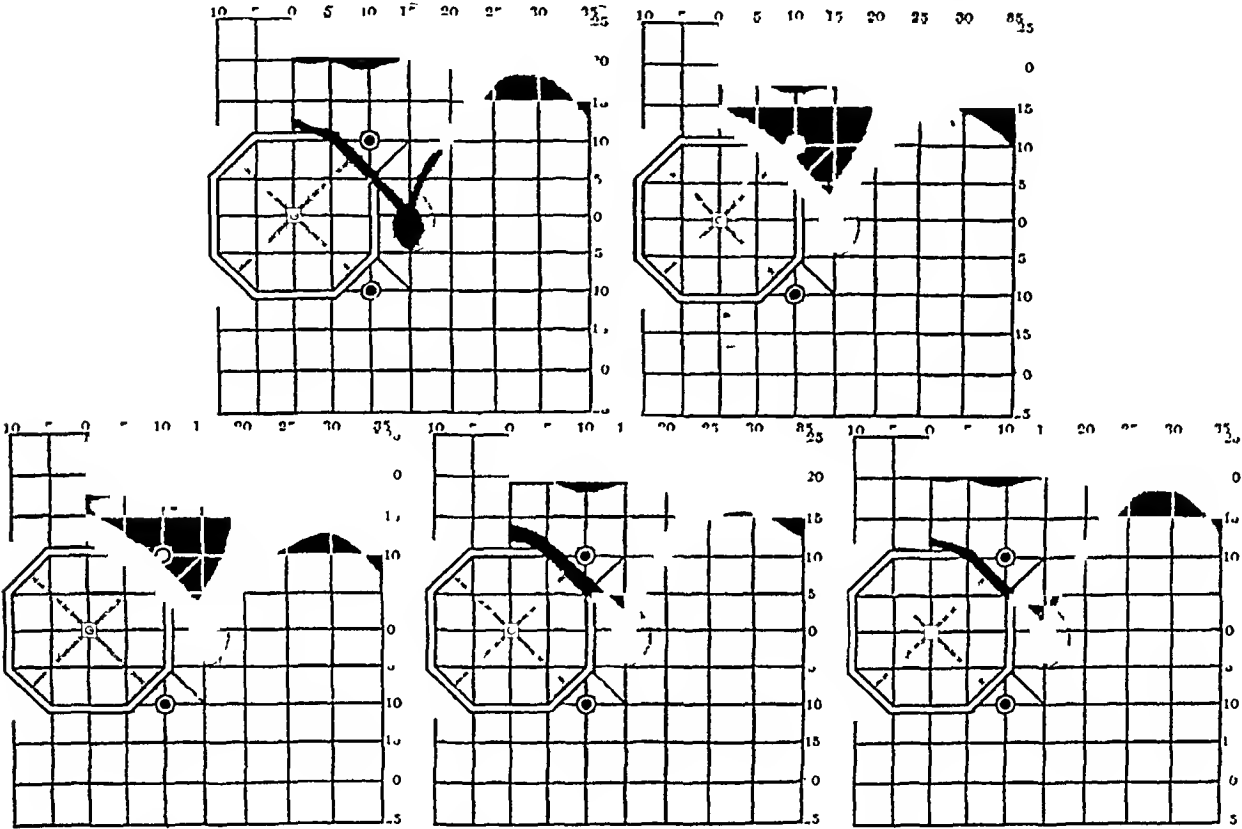


Fig 1—Angioscotomas plotted to show effects on T G of smoking a popular brand of cigaret (see table 2)

angioscotoma. There was no change in the area of the blindspot. Pupillary changes were not detectable by available methods. The first effects

were noted (table 1) from two to twenty minutes after smoking. The average time was nine minutes. Maximum effects were obtained from

TABLE 1—Appearance and Duration of Changes in the Scotoma Produced by Smoking a Popular Brand of Cigaret

Subject	First Change, Min	Maximum Effect, Min	Effect Lost, Min
G F	15	25	65
C B	2	17	107
V K	5	20	65
T G	3	18	61
O S	20	40	91
Average	9	24	78

were noted (table 1) from two to twenty minutes after smoking. The average time was nine minutes. Maximum effects were obtained from

TABLE 2—Effects of Smoking a Popular Brand of Cigaret on Subject T G

Time	Blood Pressure	Pulse	Scotoma Units
8 25	120/68	86	95
8 45	118/74	98	153
9 00	120/76	88	182
9 25	120/76	86	124
9 43	120/80	80	95

was apparently normal, as demonstrated by a complete Army physical examination one month prior to the test. The habit of smoking was well established with the subject. He smoked an

average of 20 cigarets a day. He had not smoked for two hours previous to the time the test was performed. The data appear in table 2. No untoward effects were noted.

COMMENT

Angioscotomas, as stated previously, apparently represent modifications in the functions of the retinal perivascular spaces. It is established that nicotine, the principal drug of tobacco, produces generalized peripheral vasoconstriction.¹² Nicotine is thought to exert its vascular effect through stimulation of the sympathetic nervous

and cones. Therefore, any interfering influence could be a factor in the production of defects in the visual fields. Since nicotine has been shown to alter the conductivity at synaptic junctions,¹¹ it would not be unreasonable to assume that this disturbance may contribute to the alteration of the angioscotoma. To summarize, then, any one or a combination of the two factors might explain the widening of the angioscotoma found in this experiment. At present studies are being conducted in the department which are expected to elucidate the matter.

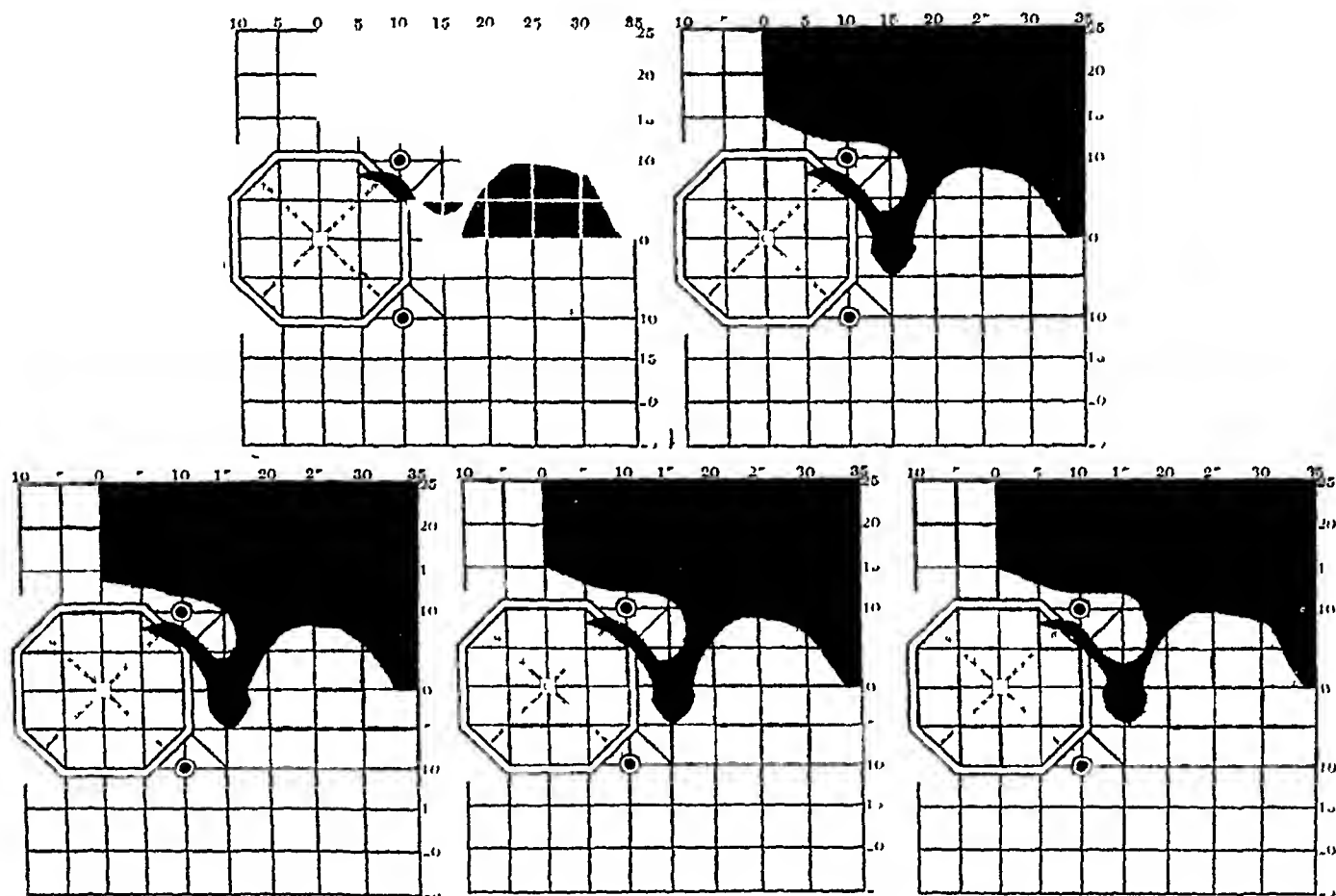


Fig 2—Angioscotomas plotted to show effects on T G of smoking a cigaret of low nicotine content (see table 3)

system, causing an increased output of epinephrine in the body. Because of this, one would expect to find a decrease in the area of the angioscotoma. Instead, widening, rather than a narrowing, was produced. There are two possible explanations for this apparent paradox. First, "Contractions of the fibers of the astrocytes, which send footplates to form the wall of the perivascular space, also increase the amount of fluid within the space by virtue of the greater cross section thus created [page 152]"¹¹ Second, it is recognized that synaptic junctions, which are very sensitive to deleterious agents, may act as a fuse to protect the layer of rods

One may speculate as to the nature of the elements found in tobacco in an attempt to understand the results obtained. Essentially, three principal constituents of tobacco must be taken into consideration: (1) nicotine, (2) tars and resins, and (3) foreign protein.

It has been believed that the foreign protein taken into the body through the mucous membrane of the respiratory tract in the act of inhalation might explain the effects of tobacco on the human circulation. However, Herrell and Cusick,¹³ who studied vascular and retinal abnormalities following the inhalation of tobacco

12 Goodman, L., and Gilman, A. *The Pharmacological Basis of Therapeutics*, New York, The Macmillan Company, 1941.

13 Herrell, W. E., and Cusick, P. L. *Vascular and Retinal Abnormalities Following Inhalation of Tobacco Smoke*, Proc. Staff Meet., Mayo Clin. **13**: 273 (May 4) 1938.

smoke, concluded that the effects produced were not related to "an allergic phenomenon or a phenomenon of sensitivity"

Tars and resins have also been suspected by some investigators¹⁴ of causing the circulatory changes produced by inhalation of tobacco Weatherby¹⁵ and Main¹⁶ demonstrated very different circulatory alterations with tobacco of high and low nicotine contents while the other two factors (proteins and tans and resins) were kept constant Haag and Larson¹⁷ obtained similar results

From the evidence presented, it would not seem unreasonable to conclude that the circulatory changes are due for the most part to the nicotine content of the tobacco The same explanation may apply to the alterations in the angioscotoma found in the present experiment, which are due to alterations in the functions of the retinal perivascular spaces¹⁰

In an attempt to understand the circulatory and vascular effects of inhalation of tobacco with respect to the nicotine content, many research

nicotine content The method, technic and procedure employed were identical with those described for the experiment with cigarets high in nicotine The results indicated (fig 3 and table 4) that cigarets containing only 0.2 per cent nicotine by weight also produced a widen-

TABLE 4—*Appearance and Duration of Changes in the Angioscotoma Produced by Smoking a Cigaret of Low Nicotine Content*

Subject	First Change, Min	Maximum Effect, Min	Effect Lost, Min
G T	2	2	18
C B	2	2	32
V K	2	2	43
T G	10	25	45
C S	5	5	20
Average	4	7	32

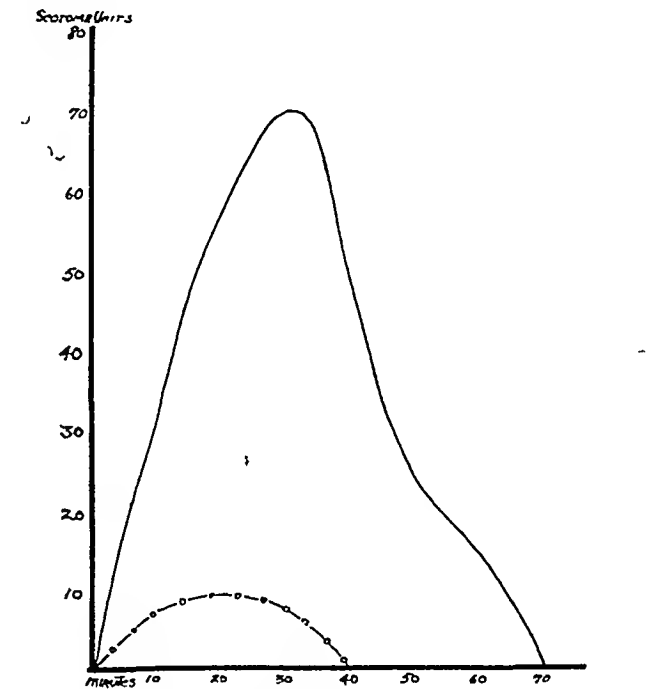


Fig 3—Effects of inhalation of tobacco, expressed in scotoma units The solid line indicates effect of smoking a popular brand of cigarette, and the line with circles, the effects of smoking a cigarette of low nicotine content

TABLE 3—*Effects of Smoking a Cigaret of Low Nicotine Content on Subject T G*

Time	Blood Pressure	Pulse	Scotoma Units
8 00	120/76	82	207
8 10	122/76	82	216
8 25	120/78	84	221
8 35	120/74	80	216
8 45	122/78	80	207

workers¹⁸ have used tobacco of low nicotine content for experimental purposes In the present work, too, for completeness of controls, it was thought necessary to carry out angioscometric studies using tobacco of low nicotine content Through the kindness of Dr H B Haag, of the Medical College of Virginia, it was possible to obtain special cigarets containing 0.2 per cent nicotine by weight The average popular brand of cigarette contains 2 per cent nicotine¹⁷

In this second series, the subjects were the same persons who had volunteered for the quantitative studies with the popular brand of cigarette They were not informed that the cigarets were low in

ing of the angioscotoma However, the alteration resulting from the inhalation of these cigarets was much less than that produced when the popular brand of cigarets was employed The first effects were noted within two to ten minutes after the last inhalation The average time was four minutes Maximum effects were obtained in two to twenty-five minutes The average time was seven minutes Eighteen to forty-five minutes after smoking the effect was completely gone The average time was thirty-two minutes The effects on the blood pressure and the pulse rate did not vary appreciably

From these studies on cigarets of low nicotine content it is possible to draw the following

14 Evans, W F, and Stewart, H J The Effect of Smoking Cigarettes on the Peripheral Blood Flow, *Am Heart J* 26 78-91 (July) 1943

15 Weatherby, J H Skin Temperature Changes Caused by Smoking and Other Sympathomimetic Stimuli, *Am Heart J* 24 17-30 (July) 1942

16 Main, R J Acute Effects of Smoking on Respiration and Circulation, *Proc Soc Exper Biol & Med* 48 495-500 (Nov) 1941

17 Haag, H B, and Larson, P S Some Chemical and Pharmacological Observations on "Low Nicotine" Tobacco, *Science* 97 187-188 (Feb 19) 1943

18 Main¹⁶ Weatherby¹⁵ Haag and Larson¹⁷

conclusions 1 Cigaretts containing one-tenth the nicotine content of the popular variety are associated with a widening of the angioscotoma 2 The degree of widening resulting after inhalation with cigarette of low nicotine value was less than that which occurred when the popular brand was employed One may assume from these observations that differences in the nicotine content of cigarette result in varied degrees of widening of the angioscotoma, provided all the other factors remain equal

A final control was thought necessary in order to determine whether the act of inhalation itself was the dominating factor in the alteration of the angioscotoma found in this experiment The subject was asked to inhale an unlighted cigarette for eight minutes This time limit was arrived at by taking into account the average time previously required to smoke the desired length of the popular brand of cigarette or the cigarette low in nicotine content The subject inhaled as often as he had been accustomed to

while smoking a lighted cigarette The results showed that in a series of 5 subjects no alteration of the angioscotoma was recognized

CONCLUSIONS

Under the conditions of these experiments and with the subjects tested the following conclusions were arrived at

1 The smoking of a certain popular brand of cigarette produces a widening of the angioscotoma

2 Cigaretts containing one-tenth the nicotine content of the popular variety produce an alteration of the angioscotoma of lesser degree than that observed with the popular brand

3 The controlled inhalation of an unlighted cigarette produced no alteration of the angioscotoma

It would seem fair to postulate that the effect on the angioscotoma was brought about by changes in the sympathetic hormonal mechanism due to the presence of the nicotine

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CYCLODIATHERMY IN TREATMENT OF GLAUCOMA DUE TO RUBEOSIS IRIDIS DIABETICA

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Rubeosis iridis diabetica is one of the most disastrous ocular diseases, for it usually involves both eyes and, with rare exceptions, causes uncontrollable glaucoma. In none of the 32 cases of this disease found in the literature could miotics control the tension. Surgical procedures, such as iridectomy (Arruga¹), iridencleisis (Kurz¹), trephination (Motolese,¹ Gallino,¹ Kurz,¹ Fehrmann,¹ Sugar¹), cyclodialysis (Salus¹) and posterior sclerotomy (Fehrmann¹), were useless, or even disastrous. The intolerable pain caused by glaucoma necessitated enucleation in several cases. Fralick,¹ in his excellent and comprehensive paper on this subject, reported on the removal of 4 eyes in 3 cases of diabetic rubeosis iridis. Any attempt to save a fraction of the vision, or even the eyeball alone, is worth while in a case of this desperate condition. In the 2 cases reported here cyclodiathermy was performed with the latter purpose.

REPORT OF CASES

CASE 1—Mrs J H, aged 28, a housewife, had the onset of diabetes at the age of 13 years. When the diabetes was first discovered, she required 70 units of insulin with a maintenance diet. Her condition improved with management, so that by the end of the first year she was taking only 24 units of insulin a day. At the age of 17 years she had acidosis, which required hospitalization. At the age of 21 the insulin was changed to protamine zinc insulin, and she required 30 units to control her diabetes. She had acute nephritis in February 1944. In January 1945 her blood pressure was 190 systolic and 110 diastolic. Urinalysis gave a 3 plus reaction for albumin, 34 mg of urea per hundred cubic centimeters, no acetone and 13 per cent of diacetic acid. The blood sugar measured 180 mg per hundred cubic centimeters when she was receiving 30 units of insulin and 100 mg when she was receiving 40 units, with a diet of 150 Gm of carbohydrate, 70 Gm of protein and 100 Gm of fat.

She came for examination of the eyes a few times after the age of 19 years, vision was normal with a correction of -0.5 D. There was no pathologic condition of the fundus in January 1942. On June 1, 1944 she stated that she had had failing vision for four months. Vision was 20/200 in each eye, with a correction of -0.50 D cyl, axis 78 it was 20/66. Both

fundi showed copper-colored arteries, very large veins and capillaries and numerous small retinal hemorrhages.

On Nov 21, 1944 vision in the right eye was limited to counting fingers at 2 feet (60 cm) and was 20/66 in the left eye. Tension was 80 mm (Schiotz) in the right eye and 22 mm in the left eye. Both disks were almost entirely covered with a thin veil of connective tissue, which extended beyond their margins. Many vessels were sheathed. There was a hemorrhage into the vitreous below the left disk. A network of vessels was present in the upper nasal section of the pupillary portion of the iris of the right eye. In another week a full picture of rubeosis iridis had developed in the right eye. On the lesser circle of the iris there was a reddish flush, produced by numerous new capillaries. Two large vessels and several finer ones radiated from the ring of capillaries to the base of the iris and disappeared behind the limbus. The pupil was round, measured 3 mm in diameter and was fixed to light. There was a hemorrhage in the vitreous of the right eye.

On Dec 8, 1944, the left iris showed a fine capillary ring in the lesser circle, and tension was over 80 mm of mercury in each eye. There was no perception of light in the right eye, and vision in the left eye was limited to perception of hand movements. Pilocarpine, neostigmine, cocaine and epinephrine, and drops of eucatropine were tried, but without effect on the tension or on the pain. The cornea of the right eye became smoky, and sometimes, with the eye stone hard, the pain was unbearable.

On Feb 9, 1945 there was no perception of light in either eye. Perforating cyclodiathermy was performed around the upper half of the cornea of the right eye, and three weeks later around the lower half. The Walker apparatus was employed, using a Weve needle with a 1 mm point, and fifty-five punctures were made 2 to 65 mm from the limbus, with a current of 25 milliamperes. The pain disappeared immediately after the operation, and tension was 20 mm four weeks later. The left eye became stone hard. On March 21 cyclodiathermy was performed on the left eye in the sector between 2 and 8 o'clock. There has been no pain in either eye since the operation.

At the time of this report, on June 9, there is no perception of light in either eye. Tension is 9 mm in the right eye and 60 mm in the left eye. On Dec 3, the right eye was slightly shrunken, the tension of the left eye was 9 mm. The right eye has a shallow anterior chamber, a wide pupil and an atrophic iris, with ectropion uveae. With the slit lamp, only a few small vessels are visible in the iris. There are numerous small vessels immediately behind the lens, evidently a hemorrhage in the vitreous is in the stage of organization. The left eye has a normal anterior chamber and a few small vessels in the iris. The pupil is of medium width and shows a weak grayish red reflex. Gonioscopic examination reveals complete blocking of the angle in each eye.

1 For the literature on rubeosis iridis diabetica, see Fralick, F B. Rubeosis Iridis Diabetica, *Am J Ophth* 28 123, 1945.

CASE 2—Mr F S, aged 20, who had had diabetes for twelve years, consulted me on Sept 11, 1941, because of severe retinopathy. In March 1942 rubeosis iridis was noted, and tension was 56 mm in the right eye and 65 mm in the left eye. Vision in each eye was limited to counting fingers at 15 meters. In April 1942 iridectomy and iris inclusion were performed on each eye because of tormenting pain. The tension fluctuated but was high again in June 1942. On June 27, 1942 there was no perception of light in either eye. Nonperforating diathermy, with a current of 50 milliamperes, was performed on the upper half of each eye. On Sept 10, 1942 examination showed a shallow anterior chamber, a large pupil, ectropion uveae and a grayish red haze in the vitreous of each eye. Tension was well below normal. On Aug 3, 1943 both eyes showed advanced atrophy of the eyeball, a shallow anterior chamber, opacity of the lens and atrophy of the iris.^{1a}

COMMENT

Cyclodiathermy was eminently advocated for hemorrhagic glaucoma due to thrombosis of the central retinal vein by Vogt² and by Albaugh and Dunphy³. The latter used their modification of cyclodiathermy (nonperforating), among others, in 6 cases of diabetes, 5 of these were cases of hemorrhagic glaucoma, and in 4 eyes the tension was controlled with the operation. None of these authors mentioned having used the method in a case of rubeosis iridis. Meyer and Sternberg⁴ performed the cyclodiathermy as described by Vogt in an undisclosed number of cases for glaucoma associated with rubeosis iridis diabetica. "Freedom from pain nearly always occurs within thirty-six hours following surgery."

Scobee⁵ performed cyclodiathermy with success in a case of rubeosis iridis. In a man aged 31 who was suffering from uncontrolled diabetes and retinopathy rubeosis iridis and glaucoma developed in the right eye. Iridencleisis did not reduce the tension, so cyclodiathermy was done. Seven weeks after operation the tension was 25 mm. Twenty-three months later the eye was

1a Since this paper was written, a third case of the same condition has been observed in the blind right eye of M M, a man aged 62, who had had diabetes for twenty years. Cyclodiathermy was performed on June 5, 1945 for pain and tension of 65 mm with the same technic as that employed in case 1. On November 6 the tension was 42 mm, and the patient has been free from pain since the operation.

2 Vogt, A. Cyclodiathermy Puncture in Cases of Glaucoma, *Brit J Ophth* 24:288, 1940.

3 Albaugh, C H, and Dunphy, E B. Cyclodiathermy, *Arch Ophth* 27:543 (March) 1942.

4 Meyer, S J, and Sternberg, P. Surgical Management of Glaucoma in Correlation with Gonioscopy and Biomicroscopy, *Tr Am Acad Ophth* (1944) 49:147, 1945.

5 Scobee, R G. Rubeosis Iridis Diabetica, *Texas State J Med* 40:432, 1944.

slightly shrunken and painless. Guerry⁶ treated 1 eye with this condition (the right eye in case 3) by means of his novel operation, angiodyathermy, and cyclodiathermy, with the result that the tension was too low to be measured in the fourth postoperative week. In performing angiodyathermy he coagulates one of the long posterior ciliary arteries just anterior to its entrance into the sclera.

As to the extent of cyclodiathermy in cases of hemorrhagic glaucoma, I quote Albaugh and Dunphy:

We now believe that in this type [hemorrhagic] of glaucoma a cyclodiathermy of any less than one-half the globe is more often than not insufficient. However, in my second case, the surface diathermy was used only around one-half the cornea in each eye, and the result was atrophy of the eyeballs. It is possible that the diathermic coagulation included the main branches of both the nasal and the temporal long posterior ciliary artery. There is convincing experimental evidence that atrophy of the eyeball follows coagulation of both long posterior ciliary arteries (Guerry). In my first case, the eye in which, in two stages, both the upper and the lower half were treated seems to be tending toward atrophy, the tension being 9 mm four months after operation. On the other hand, one-half the circumference of the other eye was treated and the tension is 60 mm of mercury, but there is no pain. There was also slight atrophy in the case reported by Scobee. I do not know the late results obtained by Meyer and Sternberg, but these authors emphasize the pain-relieving action of the procedure. All this evidence together shows that cyclodiathermy done in a case of rubeosis iridis seems to lead easily to atrophy of the eyeball. Organization of the hemorrhage into the vitreous, so frequent during this disease, is probably a contributing factor. At first not more than one-half the ciliary body should be treated, care being taken to avoid the area of one of the two long posterior ciliary arteries. If the tension or the pain persists, another quadrant can be worked on, the remaining posterior ciliary artery being spared.

I shall not discuss here the pathogenesis of diabetic rubeosis iridis. I wish to mention only one point, namely, that the damaged kidney seems to be a predisposing factor. Among the first changes in the eye due to diabetes are the enlargement and other alterations of the retinal veins. Does the presence of a renal lesion facilitate the accumulation of substances producing the vascular damage?

6 Guerry, D, III. Angiodyathermy in Treatment of Glaucoma, *Am J Ophth* 27:1376, 1944.

In conclusion, it can be stated that after disappointing results with various types of operations, cyclodiathermy is the only procedure thus far found to lower the tension in cases of glaucoma due to rubeosis iridis diabetica. However, the treatment easily results in atrophy of the eyeball if used too extensively, particularly if both long posterior ciliary arteries are destroyed.

These vessels should not be damaged if the rule laid down by Vogt is followed, i. e., if the applications are made in front of the insertion of the rectus muscles. But even if the cyclodiathermy is not done over a sufficiently large area to normalize the tension, it does alleviate the pain. Unfortunately, the progression of the damage to the retinal vessels cannot be checked.

Old National Bank Building

OCULOMOTOR PARALYSIS WITH PARTIAL RECOVERY

REPORT OF A CASE

MAX CHAMLIN, M D

NEW YORK

Lesions of the third, fourth and sixth cranial nerves are always of interest to the neurologist and the ophthalmologist. Lesions of the third nerve, particularly, attract a great deal of attention because of the widespread distribution of this nerve. The present case is one of paralysis of the third nerve with internal and external ophthalmoplegia in which abnormal reactions to drugs were exhibited. The patient was observed over a long period, during which there was partial recovery with corresponding changes in the drug reactions and the appearance of the pseudo-Graefe phenomenon.

A white woman aged 68 was first observed at the Montefiore Hospital in January 1944. The history of her symptoms dated back to May 1943, at which time she complained of the sudden onset of pain in the left side of the head followed by gradual closing of the left eye in the next six days. Soon after the onset she was admitted to a large hospital, where the clinical picture

All the ocular muscles innervated by the third nerve were found to be paralyzed. On the patient's attempting to look to the right, the right eye rotated outward, while the left globe followed slowly as far as the midline and then stopped. This was evidently due to relaxation of the external rectus muscle alone. From this position, on her attempting to look down and to the right, the nasal pericorneal vessels along the horizontal meridian were seen to be carried downward, thus indicating intorsion of the left globe by the left superior oblique muscle. Therefore, the lateral rectus and the superior oblique were the only external muscles of the left eye that were functioning.

The left pupil did not react to light, either directly or consensually. A light thrown into the left eye, however, resulted in contraction of the right pupil.

Accommodation was tested, but the results were not conclusive. Of course, at the age of 68 there is so little accommodation that measurements are not satisfactory.

At the time I first saw the patient the neurologists made a diagnosis of cerebral aneurysm. Since the paralysis of the third nerve was so complete, it is



Fig 1—A (January 1944) complete ptosis of the left eye, B (January 1944), deviation of left eye down and out and dilatation of left pupil, C (July 1944), partial recovery of ptosis on the left side

was that of complete paralysis of the third nerve probably due to cerebral aneurysm.

The rest of her history disclosed no facts relevant to this condition. General examination revealed no evidence of syphilis, either clinical or serologic, and the blood chemistry was normal. The patient was found to have complete ptosis of the left upper lid (fig 1 A). Voluntary effort to raise the lid resulted only in a slight upward pull of the skin, and even this could easily be eliminated by pressing a finger firmly against the supraorbital ridge, thus showing that the elevation of the skin was due to action of the frontalis muscle. Even with the aid of the frontalis muscle, however, no palpebral aperture was seen. When the lid was raised for the patient, the eye was found to be deviated outward and slightly downward (fig 1 B). The left pupil was dilated to 4.5 mm, as compared with 2.5 mm on the right side (fig 1 B).

quite unlikely that the nucleus proper was involved, because any lesion extensive enough to include every part of the nucleus of the third nerve on one side would, in all likelihood, involve the fourth nerve on that side and/or some portion of the nucleus of the contralateral third nerve. Therefore, it was probably the nerve trunk proper which was involved somewhere at the base of the brain.

To localize an aneurysm exactly in the neighborhood of the third nerve trunk at the circle of Willis is, at best, difficult. According to Dandy,¹ the diagnosis of an intracranial aneurysm can be made and its exact location ascertained only by one of three methods: necropsy, operation or angiographic examination. Dandy found paralysis of the third nerve in 30 per cent of his cases of intracranial aneurysm.

From the Ophthalmological Service of the Montefiore Hospital for Chronic Diseases

Presented at a meeting of the New York Society for Clinical Ophthalmology, Dec 4, 1944

¹ Dandy, W E. Intracranial Arterial Aneurysms, Ithaca, N Y, Comstock Publishing Co, Inc, 1944, p 23

In Dandy's tables of reported cases,² the present case seems to fall most nearly among those of aneurysms of the internal carotid artery just after it has entered the cranial cavity, on its posterior aspect and in the neighborhood of the posterior cerebral arteries. It is in this particular area that the third nerve trunk is most likely to be implicated without inclusion of the fourth and sixth cranial nerves. Dandy reported 17 cases of partial or complete involvement of the third nerve by aneurysms in this area. The average age of the 17 patients was 41 years, as compared with this patient's age of

the sphincter and ciliary muscles is dependent on the cholinergic system, in the case of these muscles through the third nerve, mydriatics and miotics affecting the cholinergic and adrenergic systems were used.

Pilocarpine nitrate, 2 per cent, when instilled in both eyes contracted the right pupil from 2.5 to 1.5 mm and the left pupil from 4.5 to 2.5 mm (fig. 2). However, 1 per cent physostigmine salicylate, when instilled in both eyes, contracted the right pupil to 1.5 mm, but the left pupil remained unchanged, at 4.5 mm (fig. 2).

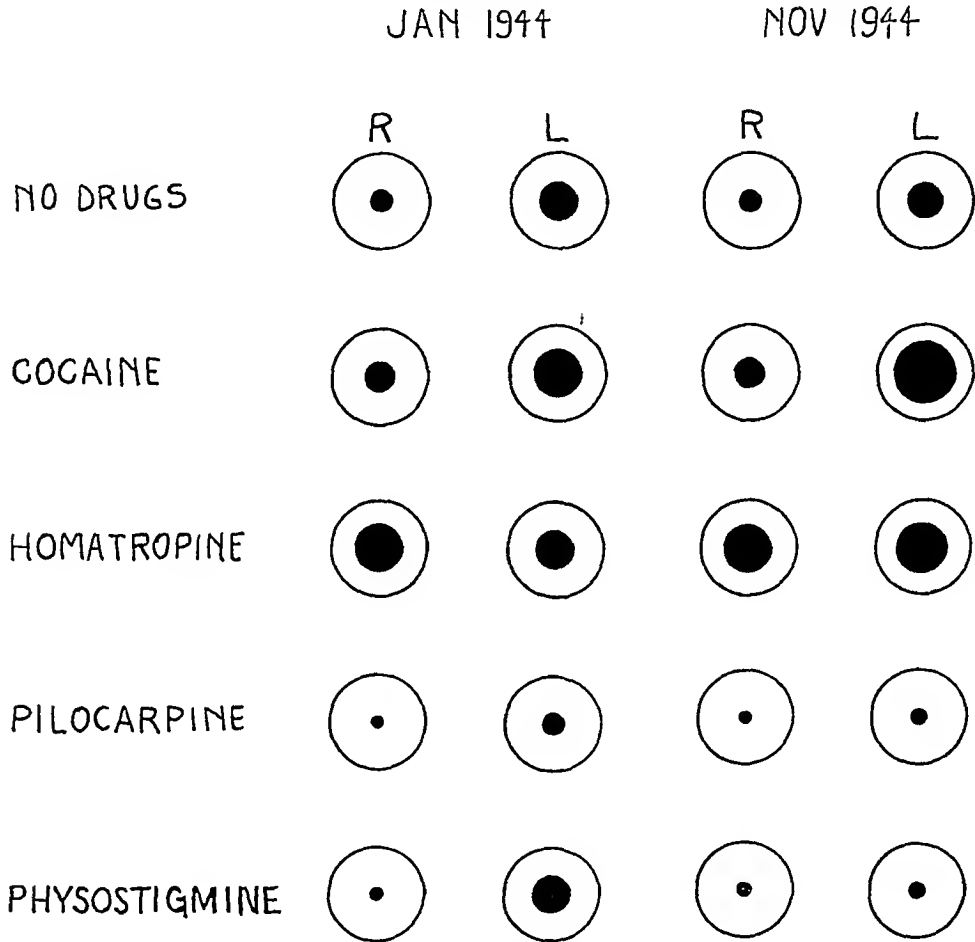


Fig. 2—Diagram representing actual size of the pupils in January 1944 and November 1944, together with the reactions to drugs. In January the left (paralyzed) pupil did not show any reaction to homatropine and physostigmine. In November, however, with partial recovery of the ptosis of the lid of the left (paretic) eye, the pupil reacted normally to these two drugs.

68 In any event, because of the complete paralysis of the third nerve and the absence of involvement of the other cranial nerves, it was thought that this patient's aneurysm was located in the internal carotid artery just after it enters the cranial cavity, in the region of the posterior cerebral vessels.

Since there was internal as well as external ophthalmoplegia, an investigation was made of the reactions of the paretic sphincter and ciliary muscles to drugs. Because the innervation of

These observations are in accord with the present day explanation of the cholinergic system, as outlined by Gifford. According to Gifford's³ table, pilocarpine acts as a choline-like substance directly on the effector unit, in this case the sphincter muscle of the iris. Therefore, even though the third nerve is defective and an inadequate supply of choline-like substance is being liberated at the myoneural junction, the direct application of the pilocarpine

2 Dandy,¹ table B

3 Gifford, S. R. *Ocular Therapeutics*, ed. 3, Philadelphia, Lea & Febiger, 1942, pp. 50 and 55.

replaces the acetylcholine and the sphincter muscle contracts. On the other hand, physostigmine acts by neutralizing the cholinesterase, which is constantly present at the myoneural junction and keeps the choline-like substance produced in check. With lesions of the third nerve, however, one may assume that choline-like substance is not being produced in sufficient quantity at the myoneural junction and that therefore, even though the cholinesterase is being neutralized by physostigmine, there is not enough acetylcholine produced by the defective third nerve to cause miosis. Thus, one can logically explain the absence of a miotic effect of physostigmine in this case. This action of physostigmine in causing acetylcholine to be made available is well known in physiology, and the experimental demonstration has been corroborated by clinical studies before.⁴

As adrenergic drugs, I used cocaine and homatropine. Cocaine dilated the right pupil from 2.5 to 3.5 mm and the left pupil from 4.5 to 5.5 mm (fig 2). When, however, homatropine was instilled into the eyes, the right pupil dilated to 5.5 mm but the left pupil remained at 4.5 mm. Here, again, my results are in accord with the action of the adrenergic system, as presented by Gifford.³ Cocaine sensitizes the smooth muscle in the dilator of the iris to the ever present sympathin E at the myoneural junction. Its action is in no way dependent on the production of acetylcholine and therefore the mydriasis with cocaine takes place. Homatropine, however, acts by preventing the action of choline-like substance on the sphincter of the iris, thus allowing sympathetic tone to dominate and thereby causing mydriasis. Here, again, since the innervation of the third nerve is defective, one may assume that acetylcholine present is insufficient in amount to be influenced by the homatropine and that, therefore, there is no dilation by the homatropine.

Thus there is an internal and an external ophthalmoplegia.

The patient was observed at intervals and showed no change in her clinical appearance until July 1944, fourteen months after the onset of her symptoms. At this time the ptosis began to diminish, the width of the palpebral fissure of the left eye measuring 3.5 mm as compared with 8.5 mm on the right side (fig 1 C). The four extraocular muscles innervated by the third nerve were still parietic. The pupil was still dilated and did not react to light (fig 2). How-

ever, when both eyes were reexamined with the miotics and mydriatics, unlike the responses in January, the reactions of the left eye to drugs were now normal, i.e., physostigmine produced miosis and homatropine mydriasis (fig 2). The persistent absence of the reaction to light may be attributed to the lack of sufficient acetylcholine for this reaction. Lowenstein and Givner,⁴ in their study of a case of cyclic oculomotor paralysis, described clinically the acetylcholine requirement of the iris for reaction of the sphincter to light. The same investigators found that when the amount of available acetylcholine was not quite enough for the reaction to light to take place, the instillation of physostigmine would make more acetylcholine available and thus help to produce the response.

With the administration of the various drugs, a study of the intraocular tension was made. Prior to the instillation of drugs the tension in the two eyes was normal and equal on all occasions. After the administration of drugs various changes were found. While these changes were not sufficiently pronounced or constant to make possible definite deductions, the reactions of the parietic eye resembled somewhat those of a glaucomatous eye. For example, in May 1944, when the pharmacologic reaction of the left eye was beginning to return to normal, both pupils contracted twenty-one minutes after the instillation of physostigmine in both eyes, but, whereas the intraocular tension in the normal eye increased from 19 to 21 mm of mercury, the tension in the parietic eye decreased from 19 to 16 mm of mercury. This test was repeated in June 1944. Eighteen minutes after the administration of physostigmine, tension in the normal eye rose from 19 to 21 mm of mercury, whereas the tension in the parietic eye fell from 19 to 14 mm of mercury.

The increase in intraocular tension following instillation of physostigmine was described by Adler⁵ as a normal phenomenon and is due to the dilatation and increased permeability of the capillaries to protein, with increased protein content of the aqueous and consequent rise in intraocular tension. On the other hand, with the contraction of the pupil of the parietic eye, the tension did not rise but actually fell. This is characteristic, rather, of the response of a glaucomatous eye. Therefore, although the parietic eye did not show any increased intraocular tension with the dilatation of the pupil, it did react to physostigmine like a glaucomatous eye, in contrast to the nonparietic eye, which reacted like any other normal eye.

⁴ Lowenstein, O. and Givner, I. Cyclic Oculomotor Paralysis, *Arch Ophth* 28:821 (Nov.) 1942.

⁵ Adler, F. H. *Clinical Physiology of the Eye*, New York, The Macmillan Company, 1933, p. 375.

Adler suggested that physostigmine may not reduce tension in cases of acute glaucoma with increased intraocular pressure and dilated pupil because the tension causes paralysis of the third nerve, that is, the defect of the third nerve decreases the production of acetylcholine and, since the presence of acetylcholine is necessary for the action of the physostigmine to take place, the physostigmine alone may not contract the pupil in acute glaucoma. While it is not suggested that glaucoma is due to paralysis of the third nerve in any form, it is shown that both conditions may respond similarly to physostigmine with respect to the intraocular pressure.

A search of the literature for other cases of paralysis of the third nerve associated with features of glaucoma revealed a case described by Smith,⁶ in which after trauma, with parasympathetic paralysis, a rise in intraocular tension was observed. If one concedes that glaucoma and paralysis of the third nerve may have common features, the next question is that of cause and effect. Thus, dilatation due to paralysis of the third nerve may produce a picture resembling glaucoma, whereas a rise in intraocular pressure may cause paralysis of the intraocular branches of the third nerve. The full explanation undoubtedly awaits much more experimental work.

Another interesting sign in the present case, noted in July 1944, fourteen months after onset of symptoms, was the "pseudo-Graefe" phenomenon, as described by the late Dr Bielschowsky.⁷ This phenomenon has been described in the stage of recovery of paralysis of the third nerve. When the patient looks down and to the nonparetic side, the upper lid of the paretic eye, instead of following downward or remaining ptosed, actually is elevated and even retracted, thus giving the impression of the Graefe sign, as seen with the exophthalmos of thyrotoxicosis (fig 3A). With this retraction of the upper lid, Bielschowsky described miosis of the paretic pupil. In the present case no miosis was observed.

According to Bielschowsky,⁷ the "Graefe phenomenon" was explained by Fuchs as follows: Because the third nerve is atrophic, an impulse intended for one muscle is likely to spread to others as well. Bielschowsky, however, expressed the belief that the phenomenon is more probably due to an actual regrowth of fibers

in the process of healing, so that the new fibers wander from the main trunk and grow into the wrong peripheral sheaths. Dandy cited Ford and Woodhall, who demonstrated this misdirection of fibers.⁸ Thus, an impulse intended for one muscle will stimulate another. Bielschowsky stated the belief that these misdirected fibers tend to follow definite paths in growing into the wrong sheaths, so that "in the majority of cases, the impulse to look down and in produces the strongest contraction of the levator of the upper lid." One should note, however, that he used the term "in the majority of cases." He explained this point, showing that even when the patient attempts internal rotation of the eyes without trying to look down, one can produce this retraction of the lid.

In the case presented here, besides exhibiting retraction of the upper lid on attempting to look down and *IN*, which is the classic picture, the patient also showed some elevation of the upper lid on attempting to look down and *OUT* (fig 3B). While the retraction in this case was not so pronounced as in the classic picture (fig 3B), it was still a definite elevation, whereas normally,

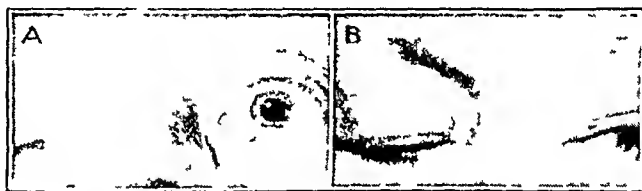


Fig 3—A (July 1944), "pseudo-Graefe" phenomenon. The patient is attempting to look down and to the right, with the right (normal) eye in that position. With the attempt to turn the paretic (left) eye down and in, the paretic lid, instead of being lowered, actually undergoes marked retraction. B (July 1944), patient attempting to look down and to the left, with the right (normal) eye in that position. With the attempt to turn the left (paretic) eye out and down, the paretic lid is raised.

on the subject's attempting to look down and *OUT*, the lid would move down with the globe. Some elevation or retraction of the left upper lid was produced in directions of gaze other than the two just mentioned.

SUMMARY

A case of internal and external ophthalmoplegia due to paralysis of the third nerve is described.

Because of the internal ophthalmoplegia, an opportunity was afforded to study the effects of various drugs on the paretic pupil during the

⁶ Smith, H. J. *Am J Ophth* 25:211 (Feb.) 1942.

⁷ Bielschowsky, A. *Lectures on Motor Anomalies*, Hanover, N. H., Dartmouth College Publications, pp 83 and 84.

⁸ Dandy,¹ pp 11 and 12.

paretic stage as well as during partial recovery. The reactions observed fit well into the present day concept of the mode of action of the cholinergic and adrenergic drugs.

Since the light reflex had not returned at the time that the normal pupillary reactions to homatropine and physostigmine did, one may assume that a stronger cholinergic tone is necessary for the light reflex than that required to produce reactions to these two drugs.

While there was no increase in intraocular tension, the reaction to physostigmine resembles that of a glaucomatous eye.

The "pseudo-Graefe" phenomenon seen in the stage of recovery of paralysis of the third nerve is illustrated. This retraction of the paretic lid can be produced by having the patient attempt to look in directions other than the classic "down and in."

1840 Grand Concourse

CONGENITAL RETINAL FOLD

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Congenital retinal fold has been reported so infrequently and on such occasions has been explained so incompletely, with so much room for questioning, that any report of a case which might suggest one further point in its development would seem to be welcome. The cases reported of this condition are so few that the presentation of almost any new case should add some new feature, or at least lead to discussion or modification of the present concept of the anomaly. After a review of some of the cases in the literature a few variations seem to present themselves in the 2 cases reported here. Subsequent study might be directed particularly along such lines.

Pathologic material was obtained in many of the early cases, since the eye was enucleated for supposed glioma and only on histologic study was the true nature of the "pseudoglioma" worked out. The name "congenital falciform ligament" was taken from the "falciform process" found in the teleostean eye, which this anomaly resembles and the resemblance to which caused Mann to suggest that the condition was of atavistic significance.

REPORT OF CASES

CASE 1—A 26 year old man stated that he had been unaware of the poor vision in his left eye until he was 11 years old, at which time he was involved in an automobile accident. After the accident his vision was tested and found to be poor. The accident did not require hospitalization, and there was no serious head trauma. The patient continued to believe that the poor vision in the left eye was the direct result of this trauma, for he had not been told otherwise. In the ensuing years he did not notice any change in this eye, there was at no time any indication of an inflammatory process developing in the eye.

All members of his family, which included his parents, 2 brothers and 2 sisters, wore glasses, but no one had vision which could not be improved with glasses. The family history was negative for congenital anomalies, as well as for all types of apparent ocular disorders.

When the patient's mother was five months pregnant, she had a severe attack of measles, during which she remained in bed for two weeks. The attack was a serious one, in her own words, "The measles settled in my head, and it was three months before I could hear again. I had a head specialist during this time to treat my head. I can't quite remember how high my fever was, but I know it was 102 or 103 [F] for

quite some time." She also stated that until he was 16 years old she had been unaware of her son's inability to see out of one eye.

The patient also had impairment of hearing in his left ear of many years' duration, which he believed to be nonprogressive. There were no other physical defects of any significance.

The fundus of the left eye showed the unusual picture illustrated in figure 1. The main feature was the large white, falciform mass stretching from the upper to the lower portion of the retina in the 1 to 7 o'clock axis. This mass was well anterior to the retina but stretched back to form an attachment with the retina except at its free ends. It overhung the disk, so that only a small portion of that structure could be seen unless an attempt was made to look around the fold. In this case the disk appeared to have a rather sharp anterior edge except at its lower extremity, where it rotated, becoming somewhat shelved, and then frayed out into multiple dentate processes, which blended indistinctly into the vitreous. The superior portion of the fold was nodular and clubbed. Its termination also suggested an imperceptible blending into the vitreous. The fold was grayish white and seemed to be striated, much as the retina appears when medullated. There were no grooves in the fold and no signs of any patencies or foramina as the nerve head was approached. The entire fold was avascular. The light from the ophthalmoscope threw a shadow along either side of the falciform ligament. There was no attachment of the fold to any portion of the lens. The fold had a slightly sinuous arrangement.

The disk, which could be seen only partially, was pinkish yellow and approximately three times the normal size of the disk. Arranged somewhat obliquely, it gave the appearance of having been drawn out irregularly by traction of the congenital retinal fold. Its margins were scalloped but not indistinct. The pattern of the blood vessels emerging from the disk was atypical and nondescript. Some of the vessels coursed along the lateral walls of the congenital fold. In general the vessels were anomalous in size and distribution, so that in many places the artery could not be distinguished from the vein. The over-all pattern of the blood vessels tended toward a paucity of vascularization throughout the fundus, which feature has been pointed out as a characteristic of the condition¹. At no place along the retinal fold did a vessel cross its sharp edge. A small round, white lesion, about the size of the disk, was present just below the macula. This lesion was horizontally oval and had a densely pigmented crescent bordering its upper edge. Many vessels, both large and small, coursed through it. One large vessel, passing inferiorly and nasally, had a pronounced parallel sheathing. Just above and slightly nasal to this lesion was a small crystalline, yellowish

1 Gartner, S. Congenital Retinal Folds and Microcephaly, Arch Ophth 25 93 (Jan) 1941

lesion with pigment granules within its center. The retina in general had a slightly atrophic appearance with many areas of dense pigmentation, together with regions where a peculiar sheen was prominent. Physical examination was noncontributory except that a decided tilt of the head to the left could not escape notice. There were no abnormalities of the heart, lungs, extremities or abdomen. Examination of the eyes showed nothing unusual except for the fundus of the left eye. The muscles, pupil, iris and lenses showed no abnormalities in either eye.

CASE 2—J. G., aged 17, was first seen at the ophthalmic clinic on Jan. 10, 1934, having come to the hospital primarily to seek aid for a pronounced con-

almost horizontally and broadening out like a champagne glass from its stem (fig. 2). The mass, which was cylindric, seemed to draw the underlying retina to it in the form of a tent. Many old pigmented choroidal patches, dark brown and irregular in shape, were present on each side of the mass, and other pigmentary blotches were present in various parts of the tentorial elevation, pigment being much more pronounced in the area closest to the large funnel-like mass. Just beyond the temporal margin of the disk was an oblique cleft through which two large vessels passed, these vessels ran up the entire length of the mass and divided into many small twigs, some of which were unusually tortuous. A few twigs also ran up the under surface of



Fig. 1 (case 1)—Retinal fold extending on both sides of the optic disk, with a large macular lesion and obstructed vessel.

vergent squint of the left eye. The patient stated that this eye had been turned in, with poor vision, all his life. He had worn glasses since the age of 4, although they seemed not to help his vision or his appearance.

Vision was restricted to light perception in the left eye and was 20/20 in the other eye. The left eye had a marked "in-shoot," with a tendency to left hyperopia. On examination with the slit lamp, both eyes showed a fairly well developed persistent pupillary membrane. The right fundus was not unusual in any respect. The left fundus presented a large whitish gray, funnel-like mass, which began just temporal to the disk and extended to the postlental region, running

the mass to terminate in some of the folds of that structure. In general, the vasculature of the fundus was not anomalous, neither was the disk or the physiologic cup strikingly unusual.

The white, funnel-like mass could not be followed to its most peripheral location, but no abnormality could be found in either lens. There were no other ocular abnormalities. The patient knew little about his parents and his brothers' eyes but believed there was nothing abnormal in any manner in these persons. Unfortunately, none of his kin were examined.

COMMENT

Congenital retinal fold is justifiably a reportable condition, for its existence has been recorded not much more than thirty times, the first report in the American literature appearing in 1940.² The majority of cases have been reported by Mann³ and by Weve⁴—a total of 14 cases being listed by these authors. The series of cases analyzed by Mann were studied primarily from the embryologic and histologic points of view, since some of the patients were not seen clinically but only pathologic specimens were received,

Weve's theory, viz, that these folds are formed by adhesions of the primary vitreous to the mesoderm of the anterior half of the eye, is essentially the same as Mann's theory of the adhesion of the primary vitreous to the inner margin of the optic cup. Weve placed emphasis on the fact that the central retinal fold was bilateral, symmetric, familial and frequently associated with other congenital anomalies. He eliminated trauma and inflammation as possible causes and corrected Tillema's⁵ misunderstanding with regard to an inflammatory origin. Weve expressed the belief that the folds were the results of traction and

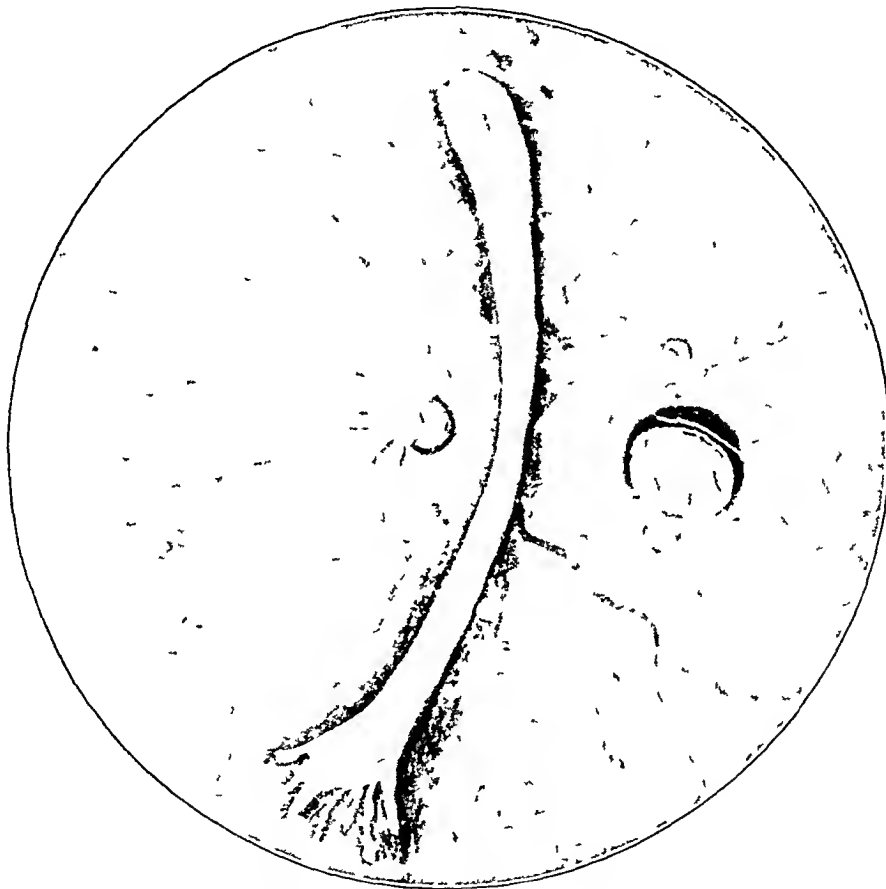


Fig 2 (case 2)—Funnel-like retinal fold extending from the disk to the lens

together with notations from the referring physicians. Weve's⁴ studies, on the other hand, were conducted along clinical and genetic lines, with a careful consideration of familial factors. These two different avenues of approach explain in some manner the theoretic promulgations made by these authors, yet they are much alike.

2 Theodore, F. H., and Ziporkes, J. Congenital Retinal Fold, *Arch Ophth* 23 1188 (June) 1940

3 Mann, I. (a) Congenital Retinal Fold, *Brit. J. Ophth* 19 641 (Dec.) 1935, (b) Case of Congenital Abnormality of Retina, *Tr. Ophth. Soc. U. Kingdom* 48 383, 1928

4 Weve, H. Ueber "Ablatio falciformis cong.," *Arch. f. Augenh.* 109 371, 1935, *Ablatio Falciformis Congenita (Retinal Fold)*, *Brit. J. Ophth* 22 456 (Aug.) 1938

that there were several varieties of this condition, some of which might come under the heading of forme fruste. These various forms include "ablatio pellucida," "ablatio falciforme," "congenital flat detachment" and "pseudoglioma" and, according to Weve, are all varieties of the same congenital condition. This author stressed the fact that the fold was usually located inferotemporally and was generally bordered by heavy pigment.

Mann³ stated that congenital retinal fold develops early, probably before the 13 mm stage, before the formation of the secondary vitreous, when the cleft is just closing and the retinal

5 Tillema, A. Infantile and Congenital Retinal Fold, *Brit. J. Ophth* 21 94 (Feb.) 1937

layers are still undifferentiated. The hyaloid system seems to hinder the formation of the secondary vitreous. In all of Mann's sections traces of the contents of the primary vitreous were adherent to the fold and in all cases the fold involved the inner layer of the optic cup. In these case reports the solid appearance of the septum, the presence of branches of the retinal artery on the fold, the attachment anteriorly to the ora serrata and the passage of strands to the lens near the equator were pointed out as definite characteristics. In all cases strands of persistent embryonic vessels were supposedly adherent to the surface of the fold. From histologic studies Mann stated^{3a}

It is quite evident that the condition is a double fold of retina pulled inwards and attached to an abnormally persistent hyaloid. The inner layer of the optic cup is alone involved in the fold, the pigment epithelium being unaffected. In all cases examined microscopically the whole of the retina shows imperfect differentiation. We are dealing with a disturbance of growth of the whole of the inner layer of the optic cup at an early age.

The three main considerations emphasized by Mann from the embryologic standpoint were the nature of the tissue in the retinal fold, the relation of the retinal fold to the hyaloid artery and the position of the fold. She offered no explanation of the cause of vitreous adhesions. Although hemorrhage at an early stage could not be excluded, the bilateral symmetric and hereditary nature of the condition in some of the cases seemed to rule out such a causative element.

The recent studies of Gregg⁶ and Swan and associates,⁷ showing the production of congenital cataract in infants whose mothers had contracted rubella in the early months of pregnancy point to the increased susceptibility of embryonic tissues particularly to virus infections. These authors stated the belief that susceptibility is fairly well limited to the first three months of pregnancy at which time the virus penetrates the chorionic barrier with ease. After that period the placenta forms and acts as a barrier to the virus.⁸ The mother of my patient (case 1) was about five months pregnant when she had measles, which "settled in her head"—she could not hear for three months. The patient apparently suffered from a virus disease during or close to the fifth month of pregnancy, which produced

acute cephalalgic symptoms and which possibly was transmitted to the embryonic tissues, particularly the neuro-ophthalmologic elements.

Van Manen⁹ suggested that the congenital retinal fold is a hyperplasia of the fetal neuroglia. He stated that this glial tissue reaches its maximum extent in the fifth fetal month, forming a system of funnel-shaped sheaths around the fetal hyaloid vessels which afterward disappear. As the eye develops this abnormally persisting tissue is tightened into a cordlike structure running through the eyeball by means of the centrally pushed primary vitreous. If a fetal adhesion exists between the hyaloid vessel and the inner layer of the retina a tentlike fold will result. In van Manen's case report he attached considerable importance to this "cudgel-like" appearance and shape of the anomaly particularly with respect to the groove near the disk, through which he stated the hyaloid vascular system runs. The retina was adherent to the posterior surface of the cudgel-like mass along its entire length and was lifted up from its pigment layer like a tent. Because the father of van Manen's patient had a congenital opacity of the lens the author suggested that the same disturbance in the germ layer of the father and the son gave rise to two different congenital abnormalities of the eye, possibly the result of faulty nutrition of the lens through disturbance in the hyaloid system in the case of the father.

Theodore and Ziporkes² reported 4 cases of congenital retinal folds. In case 1 the congenital retinal fold ran on both sides of the disk, this is the only case besides the first one reported here in which this feature was shown. In case 1 of Theodore and Ziporkes there were several secondary folds. The mother of the patient in case 2 presented by these authors had congenital cataract, together with a persistent hyaloid artery, this associated anomaly adds importance from the hereditary aspect. These authors also suggested that the macula is usually poorly developed as is the retinal blood vessel system, both features being strikingly prominent in their cases. Theodore and Ziporkes, after discussing the various theories were inclined to accept the theory put forward by Ida Mann, although they could not completely disregard the familial and hereditary features pointed out by Weve. Mental deficiency was an occurrence in 2 cases, namely, in the first case reported by Guerry¹⁰ and in Gartner's¹ case. In

6 Gregg, N. M. Congenital Cataract Following German Measles in Mother, *Tr. Ophth. Soc. Australia* (1941) 3:35, 1942.

7 Swan, C., and others. Congenital Defects in Infants Following Infectious Diseases During Pregnancy, *M. J. Australia* 2:201 (Sept. 11) 1943.

8 Rados, A. Epidemic Keratoconjunctivitis and Virus Diseases of Eye, *Arch. Ophth.* 32:308 (Oct.) 1944.

9 Van Manen, J. G. Congenital Anomaly of Fundus Oculi, *Arch. Ophth.* 26:1 (July) 1941.

10 Guerry, DuP., III. Congenital Retinal Folds. Report of Two Cases, *Am. J. Ophth.* 27:1132 (Oct., pt. 1) 1944.

Guerry's second case a congenital retinal fold was present in one eye and a congenital retinal detachment in the second eye, this being the only case on record in which these two conditions were found in different eyes of the same patient. Guerry stated that this case "lends weight to Weve's conjecture that congenital retinal folds are closely related to congenital retinal detachments."

It has been pointed out that when there is a bilateral congenital retinal fold it is usually symmetric in shape and position. When this is true, it would seem that the abnormality occurred very early in the embryonic development, possibly even before the 13 mm stage, as emphasized by Mann. In the cases of a unilateral fold it is possible that the factor responsible for maldevelopment does not involve that portion of the susceptible retina or vitreous until a much later date. When the fold is unilateral, it is very likely to be taken for "glioma," since emphasis has been placed on bilaterality in the congenital condition, although this condition does not necessarily appear to be characteristic.

Both Gartner and Theodore and Ziporkes have emphasized the character of the blood vessels, pointing out several features which were pronounced in 1 of the cases reported here. These features include the anomalous size and distribution of the blood vessels, the general paucity of blood vessels throughout the fundus, the prominent attenuation of the vessels and the difficulty in differentiating the veins from the arteries. Gartner also noted the glazed, atrophic and pigmentary disturbance of the retina, which description applies adequately to our case 1. The surface of the retinal fold is supposedly grayish but becomes somewhat pink as the disk is approached. Such changes in the retina probably result from inadequacy of blood supply, which in some manner is disturbed by the abnormal fold and the abnormal hyaloid circulation. The nature of the retina in these cases may be a clue to the time of formation of the fold and, again, may explain the secondary anatomic differences in the various cases.

INTRAOCULAR PENETRATION OF STREPTOMYCIN FOLLOWING SYSTEMIC AND LOCAL ADMINISTRATION

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AND

ANNE NICHOLS, M.S.

PHILADELPHIA

Waksman and his associates have isolated two apparently related substances, streptothricin¹ and streptomycin,² from the genus *Streptomyces* which are more bacteriostatic or bactericidal for gram-negative bacilli than is penicillin. Of the two, streptomycin has been shown to be less toxic and to possess greater action against certain gram-negative and gram-positive bacteria *in vivo*.³ Streptomycin has been demonstrated to be beneficial in treatment of experimental infections due to *Proteus vulgaris*,⁴ *Pasteurella tularensis*,⁵ *Mycobacterium tuberculosis*⁶ and organisms of the Friedlander group⁷ in animals.

The streptomycin used in this study was supplied by Merck & Co., Inc., through the Committee on Medical Research.

From the Department of Ophthalmology and the Harrison Department of Surgical Research of the University of Pennsylvania School of Medicine.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

1 Waksman, S. A., and Woodruff, H. B. Streptothricin—A New Selective Bacteriostatic and Bactericidal Agent, Particularly Active Against Gram-Negative Bacteria, *Proc Soc Exper Biol & Med* **49** 207-210, 1942.

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Recently streptomycin was shown to have possible benefit in cases of typhoid infection in man.⁸

Zintel and his co-workers⁹ have shown that the concentration of streptomycin in the blood following a single intravenous injection is better maintained than that of penicillin. Detectable amounts were usually present six hours after intramuscular administration, as compared with two to three hours in the case of penicillin. Early side reactions were not alarming, and the authors observed no late toxic effects from systemic administration.

Because of the possibility of streptomycin being of value for ocular infections, it seemed advisable to determine the intraocular penetration of this compound with various modes of administration.

METHODS OF INVESTIGATION

Modes of Administration—The following modes of systemic administration of streptomycin were studied experimentally: (1) intravenous injection of 10,000 units per kilogram, (2) intramuscular injection of 10,000 units per kilogram, (3) intravenous injection of 100,000 units per kilogram and (4) intramuscular injection of 100,000 units per kilogram, of body weight.

The following modes of local administration of streptomycin were studied experimentally:

1 Instillation of 5 drops of a solution of streptomycin containing 5,000 units per cubic centimeter of isotonic solution of sodium chloride. Each drop was instilled at an interval of thirty seconds.

2 Instillation of 0.1 Gm of an ointment containing 5,000 units of streptomycin per gram of ointment base. The ointment base was a polyethylene glycol (Carbowax) and propylene glycol in equal proportion, as previously used for penicillin.¹⁰

Friedlander Group (*Klebsiella*), *Proc Staff Meet, Mayo Clin* **20** 30-39, 1945.

8 Reimann, H. A., Elias, W. F., and Price, A. H. Streptomycin for Typhoid, *J A M A* **128** 175-180 (May 19), 1945.

9 Zintel, H. A., Flippin, H. F., Nichols, A. C., Wiley, M. N., and Rhoads, J. E. Studies on Streptomycin in Man: Absorption, Distribution, Excretion, and Toxicity, *Am J M Sc* **210** 421-430 (Oct) 1945.

10 Leopold, I. H., and LaMotte, W. O., Jr. Penetration of Penicillin in Rabbit Eyes with Normal, Inflamed and Abraded Corneas, *Arch Ophth* **33**:43-46 (Jan) 1945.

3 Instillation of drops of a solution of streptomycin containing 50,000 units per cubic centimeter of isotonic solution of sodium chloride

4 Iontophoresis with a solution of streptomycin containing 5,000 units per cubic centimeter of isotonic solution of sodium chloride. A current of 2 milliamperes was maintained for three minutes. Special glass electrodes were used, as devised by von Sallmann¹¹. The negative pole was applied to the eye electrode.

In all animal experiments, rabbits of a blue-eyed or brown-eyed chinchilla strain, weighing between 2.5 to 4 Kg., were used. Samples of aqueous humor to be analyzed for streptomycin content were obtained by making a limbal puncture with a sterile 26 gage hypodermic needle and a sterile tuberculin syringe. All eyes were topically anesthetized with 2 drops of 0.5 per cent tetracaine hydrochloride a few moments before the puncture was made. In all eyes that received streptomycin locally, the cul-de-sacs were thoroughly washed with sterile isotonic solution of sodium chloride before instilling the local anesthetic.

To obtain specimens of vitreous humor the eyes were enucleated and washed with sterile isotonic solution of sodium chloride, the sclera and the chorio-retinal layers were incised with a sterile Bard-Parker knife, and the vitreous was drawn into a sterile pipet.

Specimens of secondary aqueous were obtained by reentering the anterior chambers of eyes previously used for specimens of primary aqueous humor.

Normal eyes were removed from 4 rabbits thirty minutes, two hours, four hours and six hours, respectively, after a single intramuscular injection of 10,000 units of streptomycin per kilogram of body weight. The eyes were enucleated while the animals were under ether anesthesia. These animals were then killed with intravenous injections of air. The following tissues of these eyes were analyzed for their streptomycin content: conjunctiva, extraocular muscles, cornea, lens, vitreous, chorio-retinal layers, sclera and optic nerve. There were two eyes for each time interval. The time intervals at which these tissues were tested were thirty, one hundred and twenty, two hundred and forty and three hundred and sixty minutes after administration of streptomycin. All tissues were removed with sterile technic, weighed, transferred to a mortar and ground with sand, and a measured quantity of isotonic solution of sodium chloride added. After extraction each specimen was analyzed for streptomycin content. The same procedure was repeated using intramuscular injections of 100,000 units of streptomycin per kilogram of body weight. The time intervals for the second group were thirty minutes, two hours and four hours.

All the rabbit eyes were normal except for one group in which the corneas were experimentally abraded. The epithelium was removed from these corneas by rubbing the surface with gauze. Staining with fluorescein served as a guide to the extent of denudation. Approximately one fourth of each cornea was so denuded. Six hours was allowed to elapse after producing the denudations before such eyes were used for studies of penetration.

Method of Assay—The cup method of assay was used¹². *Staphylococcus aureus* strain SM was grown

from four to six hours in Federal Drug Administration¹³ broth pH 6.8. The growth was diluted to 1:10,000 with broth. Ten cubic centimeters of this dilution was added to 90 cc of previously melted and cooled Federal Drug Administration agar of pH 7.5, containing 2.5 per cent sodium chloride. Ten cubic centimeters of the inoculated agar was added to each Petri plate by means of a sterile wide mouth pipet. Steel-beveled assay cups, 1 cm in height and 8 mm in diameter, were used. Two assay cups were placed on each agar plate. The cups were filled to the top with the standard streptomycin or tissue extract. The diffusion took place overnight in the ice box, after which the plates were incubated at 37°C for eighteen to twenty-four hours.

The diameter of the zone of inhibition was measured in millimeters with the aid of a magnifying glass. A standard curve of streptomycin in distilled water was used to determine the concentration of strepto-

TABLE 1—*Concentration of Streptomycin in the Aqueous Humor of Normal Rabbit Eyes Following Intravenous and Intramuscular Administration*

Time After Administration of Streptomycin, Min	10,000 Units per Kilogram		100,000 Units Per Kilogram
	Intra venous, Units/Cc	Intra muscular, Units/Cc	
5	1	0	
15	1	0	
30	2	0	35
60	1	1	30
120	2	8	21
180	1	6	20
240	3	4	
300	1	4	

mycin present in primary aqueous humor and in vitreous humor and in extracts of the lens and cornea. For secondary aqueous humor and all other tissue extracts a standard curve of streptomycin in normal human or rabbit serum was used. Dilutions of 1, 2, 4, 8, 10, 15, 20, 30 and 40 units of streptomycin were used for construction of the standard curve. The diameter of the zone of inhibition was plotted against the concentration of streptomycin as abscissa. An extract of each tissue was prepared by grinding it in 0.5 cc of distilled water in a sterile mortar. Two or more cups were set up for each extract.

RESULTS

In table 1 are listed the concentrations of streptomycin in primary aqueous humor of normal rabbit eyes following a single intravenous or intramuscular injection of streptomycin. When the amount injected amounted to 10,000 units per kilogram of body weight, comparable to a single intravenous injection of 600,000

12 Stebbins, R. B., and Robinson, H. J. A Method for the Determination of Streptomycin in Body Fluids. *Proc Soc Exper Biol & Med* 59:255, 1945.

13 Ruehle, G. L. A., and Brewer, C. M. United States Food and Drug Administration Methods of Testing Antiseptics and Disinfectants, Circular 198, United States Department of Agriculture, December, 1931.

11 von Sallmann, L. Personal communication to the authors.

units in the average adult, streptomycin could be detected in the primary aqueous humor. It appeared in the aqueous humor within five minutes after the intravenous injection and could still be detected five hours later.

When the intravenous dose was raised to 100,000 units per kilogram, the concentration of streptomycin in the primary aqueous humor increased notably.

TABLE 2—Concentration of Streptomycin in Secondary Aqueous Humor of Rabbit Eyes Following Systemic Administration of 10,000 Units per Kilogram of Body Weight

Time of Withdrawal of Secondary Aqueous Humor After Administration of Streptomycin, Min *	Intravenous,† Units/Cc	Intramuscular,† Units/Cc
65	20	13
120	10	12
180	6	8

* All specimens of primary aqueous humors were withdrawn five minutes after administration of streptomycin.

† Each level represents the average values for two eyes.

Intramuscular administration of 10,000 units of streptomycin per kilogram of body weight produced detectable concentrations of streptomycin in the aqueous humor sixty minutes after the injection. Streptomycin was still definitely present in the aqueous humor five hours after the intramuscular injection.

In table 2 is recorded the concentration of streptomycin in secondary aqueous humor. A single intravenous or intramuscular injection

TABLE 3—Concentration of Streptomycin in the Aqueous Humor of Human Eyes Following a Single Intravenous Administration of 600,000 units of Streptomycin

Patient	Ocular Condition	Units of Streptomycin per Cc of Primary Aqueous Humor Withdrawn 30 Min After Intravenous Injection	Units of Streptomycin per Cc of Secondary Aqueous Humor Withdrawn 3 Hr After Initial Puncture of Anterior Chamber	Units of Streptomycin per Cc of Blood at Time of Initial Puncture of Anterior Chamber
S W	Absolute glaucoma	3	19	75
M G	Normal	1	3*	75
J G	Absolute glaucoma	3	10†	40

* Specimen taken ninety minutes after initial puncture of anterior chamber.

† Specimen taken thirty minutes after initial puncture of anterior chamber.

of 10,000 units of streptomycin per kilogram of body weight produced high concentrations of streptomycin in the secondary aqueous humor. (Compare with values in table 1.)

In table 3 are listed the concentrations in the aqueous humor in 3 human eyes following

a single intravenous administration of 600,000 units of streptomycin. Streptomycin was detectable in the primary aqueous humor thirty minutes after the intravenous injection and was increased in the secondary aqueous humor in each instance.

A single intravenous injection of 10,000 units per kilogram of body weight failed to produce detectable levels in the vitreous humor. A similar dose administered intramuscularly did produce detectable concentration in the vitreous humor two hours after the injection. By increasing the dose of streptomycin to 100,000 units per kilogram for intravenous injection, definite concentrations of streptomycin were noted in the vitreous humor. The data are listed in table 4.

A single intramuscular injection, 10,000 units of streptomycin per kilogram of body weight, produced measurable concentrations of streptomycin in the conjunctiva, extraocular muscles

TABLE 4—Concentration of Streptomycin in the Vitreous Humor of Normal Rabbit Eyes Following Intravenous and Intramuscular Administration

Time After Administration of Streptomycin, Min	10,000 Units per Kilogram		100,000 Units per Kilogram Intravenous, Units/Cc
	Intravenous, Units/Cc	Intramuscular, Units/Cc	
5	0	0	1
15	0	0	3
30	0	0	2
60	0	0	1
120	0	1	
180	0	1	
240	0	3	0
300	0	1	4

and sclera within thirty minutes, and streptomycin was present in these tissues for almost four hours. A detectable level was found in the chorioretinal layers only at two hours after such a dose (table 5). When the intramuscular dose was increased to 100,000 units per kilogram, the amounts of streptomycin in the conjunctiva, extraocular muscles and sclera were greatly increased, and levels were also obtained in the specimens of the chorioretinal layers, optic nerve and cornea. The concentrations reached were greatest in the conjunctiva. The extraocular muscles, the sclera, the chorioretinal layers, the cornea and the optic nerve showed decreasing amounts of streptomycin, in the order given. None was found in the lens. The graph demonstrates the relative concentrations in the ocular tissues after a single intramuscular injection of streptomycin.

LOCAL ADMINISTRATION

From the results recorded in table 6 it is evident that local application of solutions con-

taining 5000 units of streptomycin per cubic centimeter of isotonic solution of sodium chloride or of an ointment containing 5,000 units per gram of base penetrated into the aqueous humor of rabbit eyes with normal corneas in barely detectable amounts. Increasing the concentration of the solution to 50,000 units per cubic centimeter failed to increase the rate or the quantity of penetration. However, in eyes with corneal abrasions, the solutions containing 5,000 units per cubic centimeter of isotonic solution of sodium chloride and the ointment containing 5,000 units per gram of base pro-

raising the systemic dose from 10,000 to 100,000 units per kilogram of body weight. Likewise, the levels of streptomycin in the conjunctiva, sclera and extraocular muscles were considerably increased by using 100,000 units instead of 10,000 units per kilogram. With the larger dose, streptomycin was found in the cornea, optic nerve and chorioretinal tissues of the normal eye but not in the lens.

Quite likely the intraocular penetration of streptomycin will prove to be enhanced in eyes with inflammation. This is suggested by the notably increased concentrations of streptomycin

TABLE 5—Concentration of Streptomycin in the Ocular Tissues of Rabbits Following a Single Intramuscular Injection of Streptomycin Consisting of 10,000 or 100,000 Units per Kilogram of Body Weight

Tissue	30 Minutes After Injection		120 Minutes After Injection		240 Minutes After Injection		360 Minutes After Injection, of 10,000 Units/Kg
	10,000 Units/Kg, Units/Gm Wet Weight	100,000 Units/Kg, Units/Gm Wet Weight	10,000 Units/Kg, Units/Gm Wet Weight	100,000 Units/Kg, Units/Gm Wet Weight	10,000 Units/Kg, Units/Gm Wet Weight	100,000 Units/Kg, Units/Gm Wet Weight	
Conjunctiva	8	18	10	35	1	37	1
Extraocular muscles	2	15	8	30	1	40	1
Cornea	0	0	0	1	0	1	0
Lens	0	0	0	0	0	0	0
Chorioretinal layer	0	0	1	1	0	4	0
Sclera	4	3	1	28	1	28	0
Optic nerve	0	0	0	1	0	1	0

TABLE 6—Concentrations of Streptomycin in Aqueous Humor of Rabbit Eyes Following Local Instillation of Streptomycin in Solution and Ointment Vehicles

Time of Puncture of Anterior Chamber After Instillation of Streptomycin, Min	Streptomycin Solution,* 5,000 Units/Cc of Isotonic Solution of NaCl		Streptomycin Ointment,† 5,000 Units/Gm of Ointment Base		Streptomycin Solution, 50,000 Units/Cc of Isotonic Solution of NaCl	
	Normal Cornea, Units/Cc	Abraded Cornea, Units/Cc	Normal Cornea, Units/Cc	Abraded Cornea, Units/Cc	Normal Cornea, Units/Cc	Abraded Cornea, Units/Cc
15	1	0	0	0	1	20
30	0	8	0	4	0	21
60	1	4	0	30	0	21
120	1	25	1	20	1	14
180	1	3	0	4		
300	0	1	1	1		
360	0	0	0	1		

* Instillation of solutions consisted in administration of a total of 5 drops, 1 every thirty seconds.

† Each instillation of ointment consisted of 0.1 Gm. The ointment base used was Carbowax and propylene glycol.

duced high concentrations of streptomycin in the aqueous humor. These concentrations were still higher after drop instillations of a solution containing 50,000 units per cubic centimeter.

Iontophoresis with a solution of streptomycin produced high concentrations of streptomycin in the aqueous humor. The analyses are recorded in table 7.

COMMENT

It is evident from these data that systemically administered streptomycin penetrated into the aqueous humor and, to a smaller degree, into the vitreous humor of the normal eye. The concentrations in the aqueous and the vitreous humor were increased in the normal eyes by

TABLE 7—Concentrations of Streptomycin in Aqueous Humor of Normal Rabbit Eyes Following Local Corneal Iontophoresis* with Solution of Streptomycin Containing 5,000 Units per Cc of Isotonic Solution of Sodium Chloride

Time of Puncture of Anterior Chamber After Iontophoresis with Solution of Streptomycin, Min	Streptomycin, Units/Cc
30	30
60	70+
90	70+
120	70+

* Iontophoresis consisted in passage of current of 2 mill amperes for three minutes.

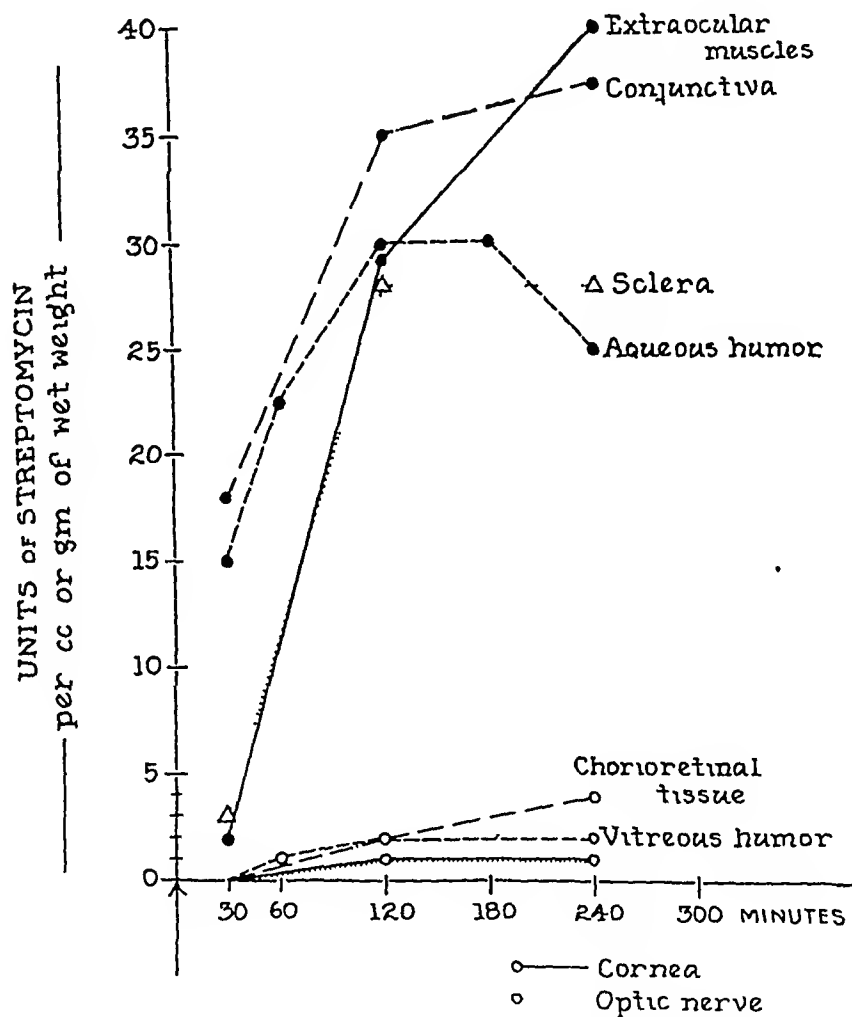
found in secondary aqueous humor of rabbit and human eyes. With this observation in mind,

it would appear that a single injection of 10,000 units per kilogram of body weight systemically administered might produce adequate therapeutic concentrations of streptomycin in the aqueous humor, conjunctiva, sclera and extraocular muscles if these parts were inflamed. However, such a dose would appear to be too small for infections of the optic nerve, chorioretinal tissue, cornea and vitreous, and a dose in the range of 100,000 units per kilogram of body weight would seem more likely to succeed. A satisfactory therapeutic level for ocular infections has not been determined as yet. Such a level will depend largely on the sensitivity

ulcer. Administration of streptomycin by iontophoresis produced fairly high concentrations in the anterior chamber. Local instillation of drops of a solution containing 5,000 units per cubic centimeter or of an ointment containing 5,000 units per gram will probably prove adequate for therapy of corneal infections due to streptomycin-sensitive organisms.

SUMMARY

A single intravenous or intramuscular injection of 10,000 units of streptomycin per kilogram of body weight produced detectable



Concentrations of streptomycin in the ocular tissues of the rabbit following a single intramuscular injection of 100,000 units per kilogram of body weight

to streptomycin in vivo of the individual causative organism. The present study simply indicates the concentrations that can be obtained in the various tissues of the normal rabbit eye and in secondary aqueous humor and may prove helpful in choosing the dose of streptomycin for therapy.

The data here given have shown that locally applied streptomycin in solution and ointment vehicle penetrated poorly into the aqueous humor of rabbit eyes with normal corneas but penetrated well when the epithelial barrier was partially removed, as in corneal abrasions or

concentrations of streptomycin in the conjunctiva, sclera, extraocular muscles and aqueous humor of the normal rabbit eye.

The concentrations in these tissues were increased by raising the systemic dose to 100,000 units per kilogram of body weight. With the larger systemic dose, streptomycin also appeared in the cornea, vitreous, chorioretinal tissue and optic nerve of the normal rabbit eye.

Concentrations of streptomycin in secondary aqueous humor were greatly increased over those in primary aqueous humor after systemically administered streptomycin.

Local administration in drop form of a solution of streptomycin containing either 5,000 or 50,000 units per cubic centimeter of isotonic solution of sodium chloride or of an ointment containing 5,000 units per gram of base failed to penetrate readily into the aqueous humor of the rabbit eye with a normal cornea. However, both the solution and the ointment penetrated readily into the aqueous humor of the rabbit eye with a partially abraded cornea.

High concentrations of streptomycin were obtained in the aqueous humor of normal rabbit eyes after iontophoresis with a solution of streptomycin containing 5,000 units per cubic centimeter of isotonic solution of sodium chloride for three minutes.

Methods of administration and doses for therapeutic purposes are suggested on the basis of these studies.

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CONGENITAL CATARACT AND OTHER ANOMALIES FOLLOWING RUBELLA IN MOTHER DURING PREGNANCY

A CALIFORNIA SURVEY

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A new concept of certain congenital anomalies has developed in the past few years with the discovery of defects in babies born of mothers who had rubella during the first three months of pregnancy. It has been more than a year now since Reese¹ reported 3 cases of congenital cataracts in infants born in the United States of mothers who had rubella in the first month of pregnancy. This report followed the initial ones of Gregg² and of Swan and his co-workers,³ from Australia, who were the first to call attention to these startling conditions. Gradually cases are being recorded by other men throughout the United States, notably Erickson,⁴ of Pasadena, Calif., who reported 11 cases in October 1944, and Perera,⁵ of New York, who recently reported a case. Winter and Lucic⁶ found 9 cases in the pediatric service of a large naval hospital on the west coast.

Several questions immediately confront one in connection with this condition. Is the placental transfer of this virus something of recent occurrence, or has the virus strain been activated in some manner during the past few years to produce these anomalies? Just what is the mechanism of the production of these defects? Why are the eyes, particularly the lens, and the heart affected to a greater degree than are other organs

or tissues? Can other virus diseases suffered during these early months of pregnancy result in similar congenital defects in the offspring? What precautions should be taken in a case of rubella occurring in the early months of pregnancy to prevent such sequelae?

That the condition may not be a new one is suggested by Erickson,^{6a} who found evidence of it in persons 5 years and 16 years of age, respectively.

Several theories to explain the production of these defects have been suggested, but to date they are all founded on speculation. Much research is still necessary. Gregg² expressed the opinion that the majority of cases of rubella concerned in his study occurred during a so-called epidemic in 1940 which affected rather widespread areas in Australia. He further stated that, as reported to him by physicians who cared for the patients, the attacks were rather severe in most cases. This suggested to him that a severe toxic condition was associated with the rubella. Such toxicity certainly has not been associated with the disease in the cases seen in this part of the country. Here, the rubella has occurred in a mild, almost subclinical, form, and in many instances considerable questioning was required to bring out a history of the disease. Therefore, if the virus in the cases of rubella occurring in this country is similar to the virus of the 1940 epidemic in Australia, it would seem that it must be of an attenuated nature. The fact remains, however, that new cases of congenital defects occurring in such circumstances are constantly being reported and that their number is not decreasing.

Of interest to me in discussing cases of this condition with men who have seen many of them is the varying emphasis placed on different types of anomalies or symptom complexes by the different men. The pediatrician is impressed with the malnourished appearance of the infant at birth and with the inevitable feeding problems and lack of normal development. Ophthal-

From the Rees-Stealy Clinic

Read before the Pediatric Section, California Medical Association, Los Angeles, May 6, 1945

1 Reese, A. B. Congenital Cataract and Other Anomalies Following German Measles in Mother, *Am J Ophth* **27** 483-487 (May) 1944

2 Gregg, N. M. Congenital Cataract Following German Measles in Mother, *Tr Ophth Soc Australia* **3** 35-46, 1942

3 Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B. Congenital Defects in Infants Following Infectious Diseases During Pregnancy, *M J Australia* **2**:201-220 (Sept 11) 1943

4 Erickson, C. A. Rubella Early in Pregnancy Causing Congenital Malformations of Eyes and Heart, *J Pediat* **25** 281-283 (Oct) 1944

5 Perera, C. A. Congenital Cataract Following Rubella in the Mother. Report of a Case, *Am J Ophth* **28** 186 (Feb) 1945

6 Winter, S. J., and Lucic, H. Personal communication to the author

6a Erickson, C. A. Personal communication to the author

mologists, of course, were first impressed with the opacities of the lens, now they are beginning to find other ocular defects, such as congenital glaucoma, microphthalmos, pigmentation of the retina, corneal opacities and strabismus. The particular interest of the specialist in the anomalies which fall within his field is to be expected, but the fact remains that the condition is a generalized one affecting the entire organism, especially the eyes and heart.

As to the possibility that other virus diseases during pregnancy may cause similar conditions, one pediatrician, in her reply to my questionnaire reported a case of microphthalmos in an infant whose mother had chickenpox during the early part of pregnancy. She noted that Brennemann,⁷ in his "Practice of Pediatrics," classifies chickenpox as a virus disease.

With regard to pathologic changes present in the eye, Swan⁸ reported in detail the macroscopic and microscopic observations at autopsy in the cases of 3 infants, and Terry⁹ described the changes in the eyes of a baby who had bilateral cataract. Swan found in the left eyes of 2 infants necrosis *en masse* of the nuclear portion of the lens, disintegration of the lens fibers and replacement by vacuoles of various sizes. He noted little formation of new fibers on the posterior part of the lens, where the nucleus was in contact with the posterior capsule. In the right eye of 1 of these infants the anterior epithelial cells of the lens were larger than usual and oval, and he surmised that these cells represented futile attempts at new fiber formation. Terry noted changes throughout the entire eye bilaterally. There were small retinal ganglion cells, a poorly formed meshwork in the angle of the iris and failure of the anterior surface of the iris to undergo atrophy and to produce the usual crypt formation. The ciliary body showed lack of development, and the rods and cones of the retina were poorly developed. The most interesting change, however, was in the lens, where the fetal nucleus almost touched the anterior pole of the lens, indicating that the lens fibers in some manner were prevented from growing forward and inserting themselves in front of the nucleus. This position of the nucleus, as one can see, differs notably from that observed by Swan. In Terry's

case the mother had had rubella during the third month of pregnancy.

According to Mann,¹⁰ the preliminary lens fibers begin their development at about the 12 mm stage, when the embryo is approximately 5 weeks old, and continue until about the 25 mm stage, when the embryo is 7 weeks old. Then the secondary lens fibers start their development. The ganglion cells first make their appearance at about the 17 mm stage, when the embryo is approximately 6 weeks old. They have their origin from differentiating cells of the inner neuroblastic layer. The first appearance of the rods and cones takes place at about the 21 mm embryo stage. The mesodermal stroma of the iris begins to differentiate at the 18 to 20 mm stage, with the formation of the fetal blood supply and the appearance of the anterior chamber. Thus, it is seen that the outstanding changes noted by Terry⁹ are in structures which have their initial process of formation during the second and third months of gestation.

The anomalies in most of the cases of congenital cardiac defects reported were a widely patent ductus arteriosus and a patent foramen ovale. Swan,⁸ citing Bedford and Brown, stated that the most important period for the development of congenital defects of the heart is from the fifth to the eighth week of intrauterine life, during which time the septums are forming. Swan pointed out that this was the precise period during which the mothers in his cases suffered from rubella.

According to Brennemann¹¹ the incidence of uncomplicated congenital lesions of the heart is low, ranging from 0.9 to 6.9 per cent in several large series of autopsies on adults. In autopsies on infants and children, however, the rate is higher, owing, of course, to the fact that the life of children with the more serious cardiac lesions is brief. The incidence of congenital lesions of the heart with associated anomalies elsewhere in the body is high enough (27 per cent in Brennemann's series of cases) to convince one that the same etiologic factor is responsible for the two conditions.

Patent ductus arteriosus is one of the most frequent congenital cardiac anomalies. Normally the ductus arteriosus ceases to function soon after birth, with expansion of the lungs, and is said to be closed completely by the end of the third month. Functional closure of the foramen ovale occurs soon after birth, although anatomic

7 Brennemann, J. Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 2, chap. 3, p. 1.

8 Swan, C. A Study of Three Infants Dying from Congenital Defects Following Maternal Rubella in the Early Stages of Pregnancy, J. Path. & Bact. **51**: 289-295 (July) 1944.

9 Terry, T. L. Personal communication to the author.

10 Mann, I. The Development of the Human Eye, London, Cambridge University Press, 1928.

11 Brennemann, J. Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 3, chap. 13, p. 35.

closure requires a longer period. Patency of the foramen ovale is the most frequent congenital cardiac lesion and when it exists alone it is not of great clinical significance.

In the fall of 1944 a survey was made among some of the ophthalmologists, pediatricians and obstetricians in California to obtain an idea of the incidence of congenital anomalies among children in this state whose mothers had had rubella during the first three months of pregnancy. Replies were received from 37 ophthalmologists, 24 pediatricians and 32 obstetricians, and their data are tabulated in the accompanying tables. Undoubtedly, some duplication is present, as in cases in which the same patient may have been seen by two physicians, for example, the ophthalmologist to whom the patient was referred and the attending pediatrician, and for this reason the numbers of cases reported by the ophthalmologists, pediatricians and obstetricians respectively are given separately in table 1. Furthermore, since not all the men who

(table 1 B) and 10 cases of other congenital anomalies (table 1 C) were reported. It is in the group of ocular defects that the greatest amount of duplication probably exists. Table 2 shows that 10 cases of rubella in women during the first three months of pregnancy were reported by the obstetricians and that congenital defects were present in 6 of the children of these mothers.

TABLE 2—*Cases of Rubella in Mothers During First Three Months of Pregnancy**

Total no. of cases	10
No. of offspring with congenital defects	6
	No. of Cases
Congenital cataract	5
Congenital cardiac defect	5
Congenital mental deficiency	1

* Reported by obstetrician

Because the greater number of cases to date has been reported from the western part of the United States, one wonders whether such congenital defects are more prevalent in this part of the country or whether, like the epidemic of shipyard conjunctivitis of several years ago, which started in Hawaii, spread to the Pacific coast and thence to the rest of the United States, this condition has spread to the Pacific coast from Australia, where it was first reported, and is now making its way across the country. Further surveys will be of interest from this point of view also.

SUMMARY

A brief review of the reported cases of congenital defects in children born of mothers who had rubella during the first three months of pregnancy is given. The pathologic observations in the cases of congenital cataract and the possible significance of the time of development of these anomalies in the embryo are discussed. The results of a survey made among some of the ophthalmologists, pediatricians and obstetricians in California to obtain an idea of the incidence of cases of these defects in the state are reported.

2001 Fourth Avenue

TABLE 1—*Congenital Defects in Children Whose Mothers Had Rubella During First Three Months of Pregnancy*

	No. of Cases
A Ocular Defects	
Cataract reported by ophthalmologist	40
Cataract reported by pediatrician	35
Cataract reported by obstetrician	5
Congenital glaucoma (reported by ophthalmologist)	2
Strabismus (reported by ophthalmologist)	1
Microphthalmos (reported by pediatrician)	4
Pigmented retina (reported by pediatrician)	2
Corneal opacity (reported by pediatrician)	1
B Cardiac Defects	
Lesion reported by pediatrician	27
Lesion reported by obstetrician	5
C Miscellaneous Anomalies	
Mental retardation (reported by pediatrician)	3
Mental retardation (reported by obstetrician)	1
Severe anemia (reported by pediatrician)	1
Purpura (reported by pediatrician)	1
Microcephalos (reported by pediatrician)	1
Hypospadias (reported by pediatrician)	1
Cleft palate (reported by pediatrician)	1
Inguinal hernia (reported by pediatrician)	1

might see children with such defects were reached, the figures cannot be considered complete. In this survey, a total of 80 cases of congenital cataract and 10 cases of other ocular defects (table 1 A), 32 cases of cardiac defects

OCULAR IMAGERY

ALFRED COWAN, M D

PHILADELPHIA

In von Helmholtz's "Treatise on Physiological Optics,"¹ Gullstrand, prefacing the description of his investigations of the actual imagery of the eye, made the following statement

The theory of collinear imagery applied to objects of finite extent and stops with finite apertures, which is the basis of the expositions still to be found in modern text-books, constitutes an essentially arbitrary extension of the region of validity of these laws, inasmuch as a system of fictions had to be introduced in place of the ideal undiscovered law

A misunderstanding of what Gullstrand meant seems to have caused considerable concern among some ophthalmologists. For instance, Lancaster,² concerning Gullstrand's statement, said

Then a prophet appeared and proclaimed the errors that permeated the current belief and practice. I believe the time is ripe for teaching ophthalmologists the truth about the formation of images. The present methods of teaching that subject have been a failure

But Gullstrand did not give a better way of teaching physiologic optics, and neither has any one else. Gullstrand did not mean that what he called the "system of fictions" should be discontinued for teaching. He said, and rightly, that one should avoid overstepping the border between what is true and what is nearly true, by representing the realities as aberrations or deviations from the ideal relations of collinear correspondence. All competent teachers of physiologic optics do that.

The fundamental laws of reflection and refraction are correct, and for an infinitely narrow, paraxial bundle of rays the theory of collinear imagery is valid. Sturm's theorem, even if fundamentally false, especially in its application to the eye, is far too valuable a means of illustrating the passage of light through an astigmatic system to be discarded. No less an authority than Southall³ said

1 von Helmholtz, H. Treatise on Physiological Optics, translated and edited by J. P. C. Southall, Ithaca, N. Y., Optical Society of America, 1924, pt. 1, appendix, p. 262.

2 Lancaster, W. B. The Story of Asthenopia, Arch. Ophth. 30:167 (Aug.) 1943.

3 Southall, J. P. C. Mirrors, Prisms and Lenses, New York, The Macmillan Company, 1918, p. 535.

In spite of its limitations and admittedly imperfect representation, Sturm's conoid remains a very useful preliminary mode of conception of the character of a narrow bundle of rays.

Gullstrand also branded the nodal points, the principal planes and the principal focal planes as so much useless ballast, but not for teaching.

There is no reason that fictions should not be employed if they serve to enable the student better to understand a subject. Gullstrand himself never hesitated to use them. His schematic eye is nothing but a mathematical conception, the constants of which are calculated for an infinitely narrow, paraxial bundle of rays. Surely, no one believes that the distances of the cardinal points along the axis, measured to the thousandth and the ten thousandth of a millimeter, are meant to be actualities. The structure of his lens is purely theoretic. Even the aberration of 1 D which he gave his eye is only an approximation. He used, when it sufficed to illustrate a point, Donders' reduced eye, the simplest of all eyes, and a pure fiction. An infinitely thin lens is a fiction, but Gullstrand used it in his simplified schematic eye. A mathematical point of light is a fiction.

What Gullstrand really meant is that Gauss's theory of collinear image points and the focal lines in the conoid of Sturm hold only in the case of an infinitely narrow bundle and are not useful when applied to the actual imagery of objects of finite extent and stops with finite apertures, especially an eye. They could not be used in his special investigation of the determination of the actual pattern of the caustic of the dioptric system of the eye. In order to do this more scientifically, he made a study of the construction of a bundle of rays in general and also of the laws of optical imagery in heterogeneous mediums. Instead of the notion of focal lines, he used his method of infinitesimal, or differential, geometry. Direct examinations were carried out with what he called subjective and objective stigmatoscopy. His investigations were the most thoroughly scientific studies of the convergence of the rays in the eye, the monochromatic aberrations and the actual form of the caustic that have ever been made.

But long before Gullstrand was born Thomas Young (1801) showed conclusively that the

eye was neither achromatic nor aplanatic. Many other investigators, particularly Volkmann (1836), Donders (1864), Herman Knapp (1864) and Tscherning (1898), had already investigated the monochromatic aberrations of the eye, often with the use of a point of light. Gullstrand's objective stigmatoscopy is nothing more than a refinement of Edward Jackson's⁴ technic of skiascopy with a luminous point.

In the eye and in the most carefully corrected optical lens systems the best image of a point object is a circle of confusion, never a point. It is a small but measurable area, a diffusion image, in which there is a tremendous confusion produced by all the phenomena natural to light, but in any optical system, as well as in the eye, the distinctness of the image is inversely proportional to the resolving power, and as long as the diameter of the diffusion image is no greater than the resolving power the image will be distinct.

The eye possesses all the aberrations of a spheric lens with the added faults of the asymmetry and decentrations of the refracting surfaces and the heterogeneous nature of the media of a living organ. Modern lens designers can produce an almost perfectly corrected lens for a specific purpose. Yet, although the aberrations of a symmetric artificial optical system are relatively simple as compared with those of the eye, an artificial image-forming instrument that would correspond with and serve all the needs of a human eye is impossible to attain.

The caustic produced by the convergence of rays in the eye is an extremely intricate, three dimensional form, which Gullstrand⁵ concluded has three cusps in its meridional section. He stated that because of the complicated form of the caustic it is a mathematical impossibility for any cross section to cut the surface in a smooth curve, in the form of a circle concentric with the pupil. On the contrary, this section must be serrated everywhere or must consist of separated isolated points. He showed the aberration in the eye to be so great and the diffusion images so large that the most useful image could not possibly correspond to the narrowest cross section of the bundle, because shades of brightness are of more importance than absolute brightness. This is in agreement with Tscherning,⁶ who also stated the belief that the best visual acuity is obtained where the section of the caustic is smallest, not where the cone has the least diam-

eter (the point of the arrow). But Ames and Proctor⁷ stated definitely that the eyes they investigated focused where the cone has the least diameter. They found also that the aberration was considerably less than that given by Gullstrand. The aberrations of the eye vary with the individual, with the size of the pupil, with the intensity of illumination and with accommodation.

The results of all such investigations are interesting academically, but, whatever the shape of the diffusion image, regardless of the complicated nature of the aberrations and the intricate pattern of the caustic produced or of whether the cusp or any other part of the caustic is utilized, this image will answer the purpose of a point image as long as its diameter is no greater than the resolving power of the optical system.

The eye will choose, either by accommodation or by the selection of a lens, that part of the caustic which gives the most distinct visual acuity, and, since sharp vision is obtained only in the vicinity of the fovea, that part of the convergent pencil which best answers the purpose will be selected. Central visual acuity is dependent on the distinctness of that very small portion of the image which lies in the area of the fovea. The surrounding halo is already in the periphery and is disregarded by the eye. Also, the peculiar structure of the retina practically neutralizes marginal astigmatism, curvature of field, distortion and other faults. The modern camera lens, so marvelously designed that a clear image is produced out to the edge of the plate, does not apply to the eye. Not only would such an image be useless, it would be confusing.

The faults of the dioptric system of the eye do not interfere with distinct visual acuity. In the words of Gullstrand,^{7a}

the monochromatic aberrations are a witness for the perfection of the eye, if what is meant by the perfection of an optical instrument is good convergence of rays to the degree that is needed to obtain the greatest useful sharpness of image anything in excess of this being sacrificed in order to gain some other end.

The aberrations of any optical system increase with the diameter of the aperture. With a small pupil there are less aberration and greater focal depth, but less brightness, and if very small, even with adequate illumination, the beneficial effect of the narrow aperture is overcome by the diffraction at the edges. The pupil must be large enough to afford sufficient brightness and at the same time to allow the formation of a sharp image by the effect on the resolving power of the eye.

4 Jackson, E. Skiascopy, Philadelphia, Edwards & Docker Co., 1895.

5 Gullstrand, in von Helmholtz,¹ p. 462.

6 Tscherning, M. Physiologic Optics, translated by C. Weiland, Philadelphia, Keystone Publishing Co., 1924, pp. 129-130.

7 Ames, A., and Proctor, C. A. Aberrations of the Eye, *Am J Physiol Optics* 4 3, 1923.

7a von Helmholtz,¹ p. 443.

Theoretically, the pupil must be neither too wide nor too narrow. The resolving power is fairly constant as long as the diameter is between 3 and 5 mm (Southall⁸). Because of the peculiar nature of the eye as an optical instrument, a large pupil has little or no effect on the distinctness of the useful retinal image as long as the system is properly in focus, whether normally, by the accommodation, or by the aid of a lens. A small pupil serves its best purpose when the image is not sharply focused.

In ocular refraction the importance of the action of the pupil must not be overlooked. Only by the use of a cycloplegic can both the accommodation and the activity of the pupil be kept under control, and, theoretically, no method of refraction, objective or subjective, is absolutely reliable with an active pupil.

Since only a relatively small bundle of rays, close to the visual axis, goes to form the useful retinal image, it is often stated, and rightly, that with a large pupil the aberration at a short distance from the axis sometimes seriously interferes with the results of retinoscopy. In most cases this fault can be eliminated by having the patient fixate the center of the mirror so that the examiner, disregarding the peripheral reflexes, can measure the error along the visual axis. This cannot be done precisely with noncycloplegic methods of retinoscopy.

In any subjective examination a wide, inactive pupil is a distinct advantage. The eye, then, without the power of accommodation and without a sufficiently small stop aperture to affect either the depth of focus or the aberration, is enabled to obtain its best visual acuity only by the aid of the proper correcting glass.

⁸ Southall, J. P. C. *Introduction to Physiological Optics*, London, Oxford University Press, 1937, p. 79.

It is logical to infer from a consideration of the phenomena under discussion that objective methods for the determination of the refraction of the eye are only an approximation, in many instances a very close one, but nevertheless an approximation. In no case should the objective results be depended on when a subjective examination is possible. The most accurate measurement of the refraction is determined by that lens which produces the sharpest retinal image in the static eye. No matter what method is used, the correctness of the refraction must be measured by the lens that procures for the static eye its best visual acuity at a distance.

The ophthalmologist in the practice of ocular refraction should have a proper conception of the convergence of the rays in the eye, of the physiologic characteristics and nature of the eye in the selection of the most useful surface of the caustic, and of the role of the pupil, all in order that the eye may procure the best visual acuity possible. With such knowledge he can appreciate the marvelous adaptability of the human eye, which in spite of its many imperfections is still superior to the most carefully designed artificial instrument. Also, he will be in a position to judge for himself of the value of each procedure for the determination of the refraction. There are many useful methods, every one of which will be found to have some disadvantage in certain cases. There is no one method that should be used to the exclusion of all others, whether for the determination of the spheric or of the astigmatic error.

The closest approximation to the exact correction of ametropia should be the aim of the ophthalmologist, but his knowledge of physiologic optics will enable him not only to secure the best results but to know when further exactness is superfluous. Perfection is neither possible nor necessary in an instrument so adaptable as the eye.

1930 Chestnut Street

Clinical Notes

RETINAL VENOUS THROMBOSIS FOLLOWING REACTION TO VACCINE

Report of a Case

CAPTAIN PARKER M. HOFFMAN

MEDICAL CORPS, ARMY OF THE UNITED STATES

Venous thrombosis of the retina is a condition rarely seen in young soldiers after vaccination. This case is the first to occur in my experience and presents interesting clinical features. The earliest examination of the fundi was made one week after onset of symptoms.

REPORT OF A CASE

A 21 year old white soldier was given subcutaneous injections of 1 cc of typhus vaccine and 0.5 cc of triple typhoid vaccine (stimulating doses) on March 3, 1945. Intradermal vaccination for smallpox was also done on the same date. One year previously he had received simultaneous inoculations for cholera and typhus and, later, simultaneous inoculations for yellow fever and typhoid, without systemic reactions. He had never before been given typhus and typhoid vaccines on the same day. He had received his last previous injection of a stimulating dose of cholera vaccine on Jan 5, 1945. His first reaction to vaccine occurred after the injections on March 3 and was characterized by onset of severe aching of the muscles and joints and general prostration three or four hours after the injections. Although the temperature was not read, it is likely that a low grade fever accompanied the reaction, which had entirely subsided by the following morning. At this time he felt fine. He had an immune reaction to smallpox vaccine.

On the afternoon of the second day he first noticed blurring of vision in the inferior field, which disappeared on occlusion of his left eye. He reported to his medical officer one week later, when the blurring failed to improve. He had experienced no other ocular symptoms and felt well in general. He was admitted to the hospital for study on March 10.

Vision had always been good in both eyes, and he gave no history of previous ocular ailments or injuries. Except for a fracture of the left femur in childhood, which healed normally, he had always had excellent health. His family history was noncontributory.

On physical examination he appeared well developed and well nourished. Medical examination revealed no abnormalities of the chest, the blood pressure or the cardiovascular, genitourinary or other systems. No possible foci of infection in the teeth, throat, sinuses or prostate gland could be found. Laboratory studies, including a Kahn test of the blood, a complete blood count, determination of the bleeding and clotting times and the sedimentation rate and urinalysis, all gave results within normal limits. A roentgenogram of the

chest and the electrocardiogram were normal. The temperature and pulse remained normal.

Initial ophthalmic examination revealed vision of 20/20 in each eye. There was no evidence of trauma or disease of the external ocular structures. The pupillary reactions were normal. The media and fundus of the right eye were normal. There was mild turbidity of the vitreous in the left eye. The disk was clearly outlined, and the retinal arteries appeared of normal caliber and luster. The main superior temporal vein of the retina of the eye, together with most of its tributaries, was partially obscured, beginning 1 disk diameter above its entrance into the papilla. Portions of the veins which could be seen through the dense hemorrhages and exudates were tortuous and cordlike. The main inferior temporal and superior nasal veins presented several areas of periphlebitis at bifurcations and arteriovenous crossings. A white sheathing of the terminal tributaries of these veins by exudates was observed. The macula was not involved, although there were a few small hemorrhages just temporal to it and some very tortuous macular veins.

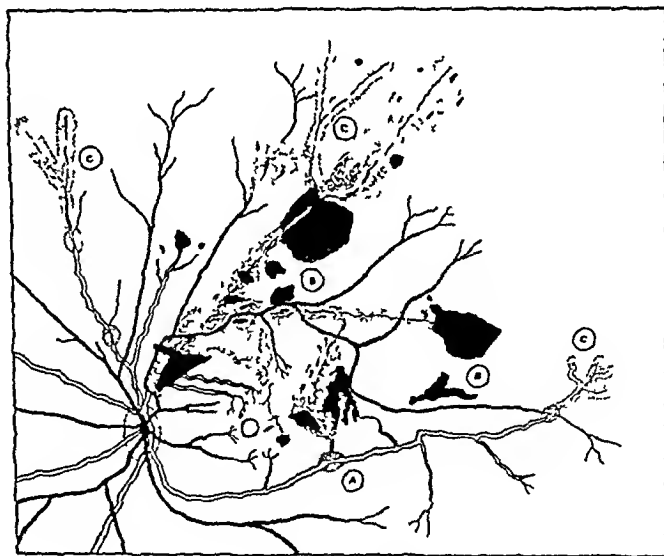


Fig 1—Early appearance of the temporal portion of the left fundus. A indicates the area of periphlebitis and the point of subsequent thrombosis, B, retinal hemorrhages, and C, perivenous exudates.

just above it. The accompanying diagram of the temporal portion of the fundus (fig 1) indicates these changes, as seen on initial examination. The intraocular tensions were normal and equal in the two eyes and remained constantly so, as determined by frequent tonometric readings.

From the initial examination and from the patient's history it was assumed that the main superior nasal and temporal veins and the main inferior temporal vein of the left eye had been attacked by an acute endophle-

bitis, the superior temporal vein having become thrombosed soon after onset of the symptoms. One week after initial examination the main inferior temporal vein became thrombosed at a point of previous constriction. Three days later signs of optic neuritis, namely, papillary edema, changes in the fields and reduced vision, of 20/100, appeared in the left eye. A week later a broad hemorrhage appeared above the macula, with small hemorrhages and pigmentary changes in the macula itself. This hemorrhage was evidently due to an extension of the thrombotic process of the main superior temporal vein to occlude completely its small central tributaries. Vision in the affected eye continued to diminish until it was limited to perception of form at 1 foot (30 cm).

The patient was treated with potassium iodide, and the older hemorrhages began to absorb. Three cervical sympathetic nerve blocks were employed for treatment of the optic neuritis. Procaine hydrochloride (1 per cent) with epinephrine hydrochloride (1:50,000) was used, with good peripheral vasodilatation. During the period of observation the disk became more sharply outlined and the blindspot assumed its normal size. The tangent screen charts (fig 2) indicate the progressive changes in the field which paralleled the rapid advance of the pathologic process. After a period of two weeks in which there was relatively little change, the patient was transferred to the Zone of the Interior for further follow-up study and treatment.

SUMMARY

The uncommon occurrence of retinal periphlebitis and progressive thrombosis in a young adult following stimulating doses of vaccines with associated anaphylactoid reaction is recorded, with a case history.

The early stage of involvement of the inferior temporal veins was apparent, and progressive thrombotic changes in the fundus and visual fields were followed. It is of interest that the superior nasal veins, although showing similar early periphlebitic constrictions and exudate, did not become thrombosed, and the exudate disappeared completely. Optic neuritis occurred in the affected eye during the third week of the disease, followed one week later by macular involvement. Intraocular tension was not notably affected during my six weeks' observation of the patient.

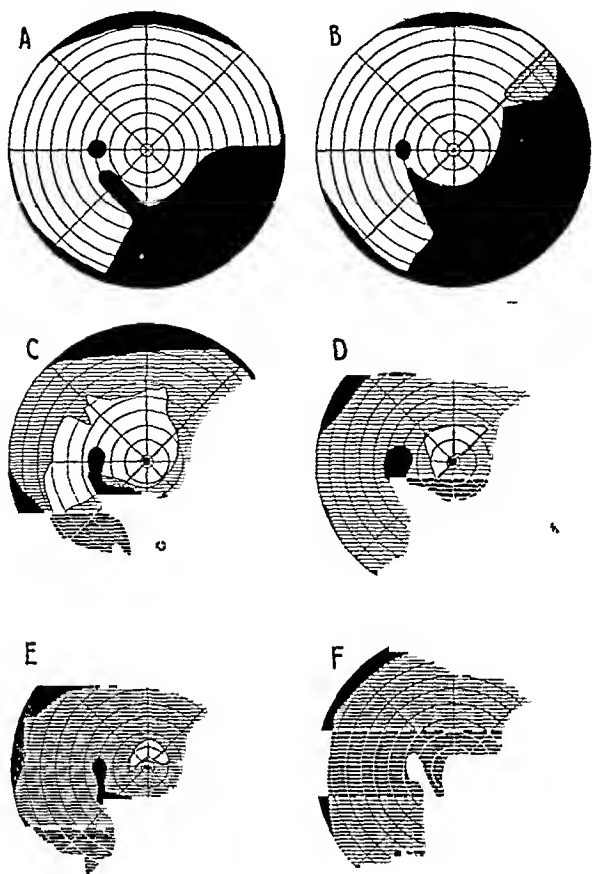


Fig 2—Visual fields of the left eye taken with the tangent screen. *A* (March 10), initial scotoma in the inferior nasal field, vision 20/20, *B* (March 17), enlargement of the scotoma with a relative component due to thrombosis of the inferior temporal vein, vision 20/30, *C* (March 21), enlargement of the blindspot, small central scotoma and peripheral contraction due to secondary optic neuritis, vision 20/100, *D* (March 23), progressive narrowing of the visual fields, vision 20/100, *E* (March 25), changes following cervical sympathetic nerve block, vision 20/200, and *F* (April 7), extension of the scotoma following thrombosis of the central tributaries of the superior temporal vein, with macular hemorrhage, vision limited to perception of form at 2 feet (60 cm). Fields *A* to *E* were taken with a 3 mm white test object and field *F* was taken with 6 mm white test object at a distance of 1,000 mm.

Clinical Notes

CORNEAL PUNCH FOR SQUARE AND RECTANGULAR TRANSPLANTATIONS OF CORNEA

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When one is performing transplantations of the cornea using a rectangular implant, a protruding lip of cornea may remain posteriorly. This condition is especially likely to be encountered when the recipient cornea is thickened or edematous. The removal of this lip with instruments ordinarily available has been found most difficult. Therefore a square corneal punch has been devised.¹ It has been in use since 1941 and has been found practical in performing square and rectangular transplantations of the cornea.

The lower blade of the punch, which is introduced into the anterior chamber, is rounded



Fig 1—Square keratoplasty punch

and dull, so that danger of injury to the lens is minimized. The double action of the cutting blade reduces the force required to snip the cornea. The punch cut is made from above downward, and the lower blade of the forceps remains stationary. After the area to be grafted

This study was aided by a grant from the Ophthalmological Foundation, Inc. Construction of the instrument was also aided by a grant from the John and Mary R. Markle Foundation.

1 The instrument was made by V. Mueller & Co., Chicago.

has been excised, any lip of cornea which remains is removed, as shown in figure 2.

The punch may be used for excising the sclera in iridocorneosclerectomy,² but the use of the rounded cutting blade previously described² is

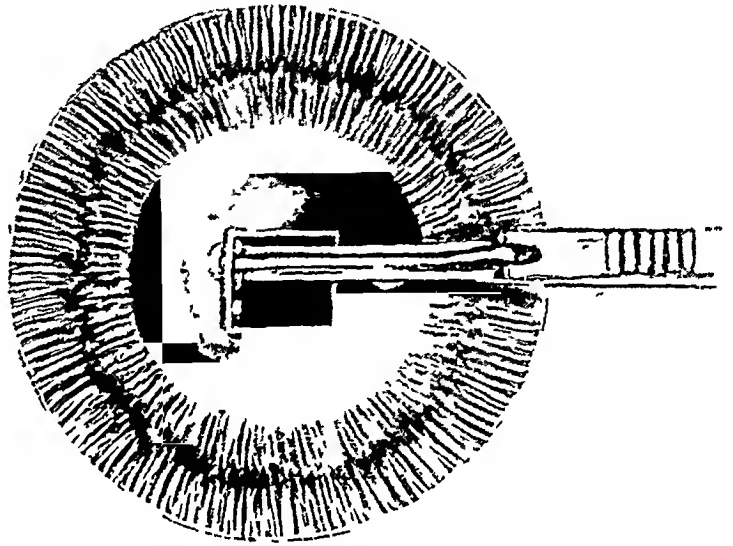


Fig 2—After the area to be grafted has been excised, any remaining lip of corneal tissue is clipped with the square corneal punch. A second bite of cornea is being excised with the punch.

preferred for sclerectomy and for the excision of irregularities in the recipient cornea when preparing for circular grafts.

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2 Berens, C. Iridocorneosclerectomy for Glaucoma, *Am J Ophth* 19 470-481, 1936.

Ophthalmologic Reviews

EDITED BY DR FRANCIS HEED ADLER

OCULAR COMPLICATIONS OF MALARIA

W MORTON GRANT, M D

BOSTON

The incidence of ophthalmic disease is significantly increased in patients with malaria, and the ocular disturbance can at times be the most serious complication of the general illness. This is an opinion borne out by more than 200 reports on the ocular complications of malaria published in the past seventy years. Certain types of ocular lesions appear to be characteristically associated with the various phases of systemic malarial infection. In view of the number of new cases of malaria now occurring as a result of military operations in the tropics, a survey of the ophthalmic aspects of the acute and the masked disease appears pertinent.

Opinions on the frequency of ocular complications in malaria have been divergent, depending considerably on variations in the definition of the term "complication" used by the different observers, as well as on the type of disease and the thoroughness of examination. In some instances "complication" has been used to signify little more than coincidence, while in others the term has been restricted to those ocular lesions which could be identified as local effects of the plasmodia. The patients described in some reports were seriously ill or were moribund. A number of factors must, therefore, be taken into consideration in examining the literature for information on those aspects which seem to be of most practical importance now, i. e., changes in eyes which may occur as the result of the development of acute or masked malaria in otherwise healthy persons. On inspection of the figures available for the incidence of ocular complications from this standpoint, it appears that the values of 10 per cent (Poncet,¹ 1878) and 20 per cent (Sulzer,² 1890), which applied to a selection of chronically and seriously ill patients, might be excessive, whereas the opinion of

Elliot,³ that ocular manifestations were rare in India, was influenced by a reluctance to consider as a complication of malaria any ocular disease unless it could be demonstrated to be caused directly by the plasmodium (by biopsy or necropsy), or at least to be cyclic in nature and alleviated by quinine. Experiences in Africa and Greece in World War I applied largely to new acute infections in Europeans acquired in the course of military migrations and should be more closely analogous to present conditions, except, of course, for current improvements in the treatment of the systemic disease. In caring for troops in Salonika, Bywater⁴ (1922) was impressed with the fact that there were comparatively many ocular complications in the cases of malaria but scarcely any in an equal number of cases of dysentery seen at the same time. Dedimos⁵ (1932), reporting in detail his observations on French soldiers infected with malaria in Macedonia, stated that the incidence of ocular complications was between 10 and 20 per cent, while Carlotti⁶ (1918), for the same period in Greece, indicated nearly 10 per cent. More recently an incidence of 15 to 20 per cent has been reported from Brazil (Fialho,⁷ 1927). On the other hand, Toulant⁸ (1938), from his experiences in a civilian hospital in Algiers with several hundred patients suffering from chronic or cachectic malaria, concluded that ocular complications were relatively infrequently attributable to malaria and that most of the ocular disease was due to syphilis, alcoholism, quinine poisoning and trachoma. In general, it would be expected that the relationship between ocular

3 Elliot, R. H. *Tropical Ophthalmology*, New York, Oxford University Press, 1920.

4 Bywater, H. H. *Notes on Malarial Conditions of the Eye*, *Tr. Ophth. Soc. U. Kingdom* **42**: 359, 1922.

5 Dedimos, P. *Les manifestations oculaires du paludisme*, *Arch. d'opht.* **49**: 166, 249 and 330, 1932.

6 Carlotti, *Troubles de l'appareil visuel attribuables au paludisme en Macedoine*, *Ann. d'ocul.* **155**: 478, 1918.

7 Fialho, A. *Manifestações oculares do paludismo*, *Arch. brasil. de med.* **27**: 162, 1927.

8 Toulant, P. *Complications oculaires du paludisme*, *Acta ophth. orient.* **1**: 18, 1938.

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1 Poncet, F. *De la chorio-retinite palustre*, *Ann. d'ocul.* **79**: 201, 1878.

2 Sulzer, D. E. *Trouble de la vision dans l'impaludisme*, *Arch. d'opht.* **10**: 193, 1890.

disease and malaria might be most clearly distinguished in young men medically preselected for military service, among whom the incidence of complicating systemic disease is normally low. Accounts of experience with ocular complications in World War II by Talbot⁹ (1943) and Robertson¹⁰ (1944) give the impression that ocular manifestations are relatively frequent, although, unfortunately, actual figures are not cited. In consideration of the opinions and evidence presented in these various reports, it seems reasonable to conclude that malaria is worthy of note as an inciter of ocular disturbances.

The several types of ocular complications which have been associated with malaria are in general described with considerable uniformity by numerous observers. The most frequent ocular complication has been considered, almost unanimously, to be dendritic, or herpetic, keratitis¹¹. This corneal disease has constituted a considerable proportion of the ocular disease associated with malaria reported by various authors from the time of its recognition in conjunction with malaria by Kipp,¹² in 1880, to the recent observations on troops in the southwest Pacific by Chamberlain and Bronson¹³. Series of cases of herpetic keratitis associated with malaria have been reported by Kipp¹⁴ (1889, 120 cases), Chavernac¹⁵ (1918, 146 cases), Bywater⁴ (1922, 60 cases), Kiep¹⁶ (1922, 63 cases) and Carlotti⁶ (1918, 46 cases). Much less often interstitial keratitis has been noted. Neither form of the corneal disease has been shown to be due to a local infection with plasmodia. More recently, herpetic keratitis was observed by Chamberlain and Bronson¹³ (1945) to occur six times as frequently in a division in which 80 per cent of the soldiers had malaria as in a comparable group which was free from malaria.

9 Talbot, D. R. New Aspects of Malaria, *J. A. M. A.* **123** 192 (Sept. 25) 1943.

10 Robertson, J. N. Ophthalmologic Lesions Encountered in Tropics, with Special Reference to Ocular Manifestations of Malaria, *North Carolina M. J.* **5** 483, 1944.

11 (a) Bispham, W. N. Malaria, Baltimore, Williams & Wilkins Company, 1944. (b) Fialho⁷. (c) Toulant⁸.

12 Kipp, C. J. On Keratitis from Malaria Fever, *Tr. Am. Ophth. Soc.* **3** 91, 1880.

13 Chamberlain, W. P., and Bronson, L. H. Herpes Simplex Keratitis in Malaria, *Arch. Ophth.* **33** 177 (March) 1945.

14 Kipp, C. J. Further Observations on Malarial Keratitis, *Tr. Am. Ophth. Soc.* **5** 331, 1889.

15 Chavernac, P. L. Les complications oculaires du paludisme à l'armée d'Orient, *Marseille med.* **55**:209, 326 and 376, 1918.

16 Kiep, W. H. Ocular Complications Occurring in Malaria, *Tr. Ophth. Soc. U. Kingdom* **42** 394, 1922.

Although this complication was found in only 1 of every 700 patients with malaria, it ranked above any other single ocular condition as a reason for limiting duty, because of persistent irritation and interference with vision. The type of malaria most commonly causing this corneal disturbance is the benign tertian form. The dendritic keratitis appears characteristically twenty-four to forty-eight hours after a first attack of malarial fever, although it also often occurs with subsequent attacks of fever or between attacks⁸. The keratitis usually occurs in one eye only, and its onset is marked by discomfort, ranging from the sensation of a foreign body to burning with photophobia and lacrimation. The cornea is hypesthetic, and the lesion stains with fluorescein in the typical dendritic pattern recognized as a characteristic manifestation of the herpes simplex virus in the corneal epithelium. The virus has been identified in the condition associated with malaria. The usual course of the keratitis in the absence of local treatment is gradual improvement over a period of approximately six weeks, with residual corneal opacification and often with recurrences of the process. Treatment of the lesion with iodine ordinarily shortens the course, and recent evidence indicates that application of sulfadiazine powder may be beneficial¹⁷. It appears likely that the hyperthermia of the acute febrile attacks may incite the corneal disease in malaria, since herpetic keratitis also occurs with other illnesses characterized by fever, such as infections of the respiratory tract, pneumonia and influenza. Another possible inciting factor, which will be discussed in more detail subsequently, is malarial trigeminal neuralgia.

Besides the herpetic keratitis already described, a type of corneal lesion referred to by most authors is described as a monocular interstitial process with clouding of the stroma but without vascularization¹⁸. However, this second type of corneal lesion appears to be relatively rare even with chronic and cachectic malaria. Severe forms of the condition have been described as keratitis profunda¹⁹ and disciform keratitis²⁰. The epithelium is said to be essentially normal except for small, subepithelial opacities or in-

17 Gundersen, T. Herpes Corneae, *Arch. Ophth.* **15** 225 (Feb.) 1936. Chamberlain and Bronson¹³.

18 (a) Blatt, N. Augenveränderungen bei Malaria, *Klin. Monatsbl. f. Augenh.* **80** 468, 1928. (b) Dedimos⁵. (c) Kiep¹⁶. (d) Bywater⁴.

19 von Arlt, F. R., cited by Fuchs, E. Text-Book of Ophthalmology, translated by A. Duane, Philadelphia, J. B. Lippincott Company, 1911.

20 Maxwell, E. M. Observations on Eye Conditions Met with in Malta, 1916-1917, *Brit. J. Ophth.* **2**:406, 1918.

filtrates in some instances⁶ The process is accompanied with intense vascular injection about the cornea Pathogenic organisms have not been found in the conjunctival sac There are photophobia, fronto-orbital pain and reduction of vision Progress is slow, the inflammation usually lasts two to three months and may leave permanent corneal opacity The nature of the pathologic processes concerned in the production of this type of keratitis is undetermined However, in view of the frequency of herpetic keratitis, it seems possible that some of the interstitial lesions may be metaherpetic sequelae¹⁷

A major proportion of the ocular complications which have been described in association with malaria are due to vascular and neurologic lesions These disturbances are apparently dependent on the pathologic changes in small vessels which are considered to be an important feature of malarial infection, especially in the more severe forms of the disease, e g, the malignant tertian type (Kirk,²¹ 1918, Bywater,⁴ 1922) The microscopic characteristics of minute foci of necrosis and hemorrhage, resulting from degenerative changes in capillary endothelial cells and obstruction of the lumen of the vessel by pigmented leukocytes and erythrocytes, have been described in the eye by Poncet¹ (1878) and in the brain by Durck²² (1925) The vascular lesions of the brain associated with malaria which are considered to be closely analogous to those of the eye have been reviewed in detail by Anderson²³ (1927) Endothelial changes are described, including phagocytic action, degeneration and hypertrophy, with capillary obstruction by parasitized erythrocytes and leukocytes, free pigment and endothelial cells The tendency to capillary thrombosis in malaria is partly explained by an increased agglutinative tendency of parasitized erythrocytes²⁴ Pigment arising from parasites and degenerated erythrocytes may be found deposited in the neighborhood of small vessels, especially in cases of chronic or cachectic malaria, but appears to be of little significance when not causing obstruction The suggestion made by some authors of a "toxic" factor in the production of injury to

blood vessels is based on the occasional observation of degenerative changes in vessel walls without thrombosis²⁵

Hemorrhages in the ocular fundus, presumably resulting from malarial alterations in vessel walls, have been noted by many observers Two types of retinal hemorrhage are usually described, the small peripheral and the large central²⁶ The latter type, which may destroy central vision, is practically limited to chronically recurring or cachectic malaria with severe anemia and appears to occur rarely at present The small type of hemorrhage, which characteristically is multiple and located in the periphery of the retina, is believed to be more common in occurrence even in the less severe malarial infections²⁷ Owing to the location of the lesions, in the neighborhood of the ora serrata, visual disturbances are not observed, and the presence of the hemorrhages themselves may not be detected unless careful ophthalmoscopic examination is made Some idea of the incidence of retinal hemorrhages in unselected cases of malaria may be obtained from the observation by Kiep¹⁶ (1922) of 10 instances of this lesion during a period in which he encountered 63 cases of malarial herpetic keratitis (among soldiers in World War I) The retinal vascular lesions have been noted most often in association with malignant tertian (tropical) malaria, and an increase in the number of hemorrhages during an acute exacerbation of fever has been frequently described^{18a} It is concluded by most observers that the small type of retinal hemorrhage is readily reabsorbed under antimalarial treatment and rarely leads to retinitis proliferans or retinal separation²⁸ When the malaria is of fatal severity, retinal hemorrhages are reported to be a constant histologic feature and are presumed to be caused by multiple embolic or thrombotic occlusions of small vessels, analogous to the process believed to underlie the formation of the cerebral petechial hemorrhages observed with this disease²⁹ Emptying of retinal vessels peripheral to emboli was described by Poncet¹ (1878) from a study of flat preparations of retinas of malarial patients, and it is possible

21 Kirk, J Malaria and Diseases of the Eye, Brit M J 2 110, 1918

22 Dürck, H Ueber die mit herdformigen Glia-produktionen einhergehenden Erkrankungen des Nervensystems, Arch f Schiffs- u Tropen-Hyg 29 43, 1925

23 Anderson, W K Malarial Psychoses and Neuroses Their Medical, Sociological, and Legal Aspects, New York, Oxford University Press, 1927

24 Bignami, A, and Nazari, A Sulle encefaliti emorragiche e sulla patogenesi delle emorragie malariche del cervello, Riv sper di freniat 62 109, 1916

25 Anderson²³ Blatt^{18a}

26 (a) Villard, H Les complications oculaire du paludisme, Arch d'opht 47 200, 1930 (b) Poncet¹ (c) Toulant⁸ (d) Blatt^{18a}

27 Elliot³ Bywater⁴

28 (a) de Andrade, C Augenabteilungen bei den Tropenkrankheiten, Arch clin oftal 4 17, 1937 (b) Motegi, A, Kan, T, Kô, S, and Syu, S Ophthalmologische Beobachtungen an 100 Fallen von Malaria-Kranken, Klin Monatsbl f Augenh 92 797, 1934 (c) Blatt^{18a}

29 Anderson²³ Poncet¹

that an apparent spasm of retinal vessels accompanying hemorrhages and amaurosis, which has been described in a few instances, may be a manifestation of such embolic obstruction, although the association of changes in retinal vessels with peripheral ischemia noted by Raynaud in a case of malaria suggested a truly spastic condition³⁰ Plasmodia have been identified in the vascular lesions of the retina by Laveran³¹ (1880) and Fisher³² (1921) and in vessels of the optic nerve and retina by Dudgeon³³ (1921)

The same kind of malarial lesions which may be found in blood vessels of the retina and brain are also found in the vessels of the choroid and optic nerve³⁴ In the fatal cases studied by Poncet¹ (1878) choroidal vessels were usually distended with erythrocytes and pigment-containing leukocytes Accumulations of extravasated phagocytic cells were present in some places Edema was conspicuous, especially in the region of the papilla In cases in which the systemic disease is of much less severity than it was in Poncet's cases, evidences of similar chorioiditis or chorioretinitis may be found clinically in the fundus in the form of edema, particularly the peripapillary type, followed in some instances by the appearance of yellowish white patches with smaller accumulations of pigment (Blatt,^{18a} 1928, Bywater,⁴ 1922) It has been claimed in several reports that simple peripapillary edema, sometimes associated with hyperemia of the nerve head, occurs in as many as 20 per cent of patients with acute recurrent attacks of malarial fever³⁵ This disturbance is usually accompanied with headache and causes no significant change in vision except enlargement of the blind-spot The same type of disturbance has been observed recently among soldiers in the tropics (Robertson,¹⁰ 1944) The changes are said to regress ordinarily when the malaria is adequately controlled

30 (a) Sedan, J Cecite temporaire par angio-spasme retinien d'origine paludique, *Ann d'ocul* **166** 705, 1929 (b) Lavagna, J Contributions a l'etude de troubles oculaires paludiques, Thesis, Faculte de Montpellier, 1920 (c) Raynaud, M, cited by Villard²⁶ (d) de Andrade²⁸

31 Laveran Deuxieme note relatif a un nouveau parasite trouve dans le sang des malades atteints de la fièvre, *Bull Acad de med* **9** 1346, 1880

32 Fisher, J H Disease of the Retina, *Tr Ophth Soc U Kingdom* **41** 235, 1921

33 Dudgeon, L S A Case of Malignant Malaria, *Tr Ophth Soc U Kingdom* **41** 237, 1921

34 Guarneri, G Ricerche sulle alterazioni della retina nella infezione acuta da malaria, *Arch per le sc med* **21** 1, 1897

35 Bushmich, D G Ocular Symptoms in Malaria, *Vestnik oftal* **17** 265, 1940 Yait, M Malarial Infection of the Eye, *Brit M J* **2** 870 1898, *Ann d'ocul* **121** 469, 1899 Motegi and others^{24b}

The vascular lesions recognized in association with malaria have also been considered to be the basis of several ocular neurologic disturbances, as well as of more general cerebral and peripheral neurologic disturbances The ocular neurologic lesions of most significance so far as they affect vision are those of the retina and optic nerve or of the pathways of the brain On the basis of clinical and histologic observations, it is generally believed that lesions in nerves may result from alterations in blood supply by vascular obstruction or hemorrhage in the same way that the neural elements of the retina may be affected Disturbances of vision are recorded as a common manifestation of malaria both in recent accounts and in reports from World War I Robertson¹⁰ (1944) reports that a frequent complaint among troops having malaria in the southwest Pacific area was the presence of scotomas or loss of vision lasting a few minutes to several hours, followed by severe headache and persistently diminished visual acuity There were attendant dizziness, orbital pain and tenderness with photophobia A similar description is given by Talbot⁹ (1943), who wrote that the only complaint of a large group of malarial patients from the same area was "visual disorders with headache, often of long duration" From their experiences in World War I, Toulant⁸ (1938) and Kirk²¹ (1918) also reported their impressions of the frequency of reduction of vision with malaria Changes in the optic nerve and in the fundus sufficient to account for the amblyopia and amaurosis have been described in some cases, while cerebral lesions have been considered responsible for the disturbances in others⁹ In addition to the cases of obvious disease, there is usually mentioned a considerable proportion of cases in which the disturbance of vision is ascribable only to refractive or accommodative changes³⁶

Those lesions resulting in loss of vision which are evident ophthalmoscopically are optic neuritis or atrophy of the optic nerve and degenerative or hemorrhagic lesions of the retina and choroid In the malarial patients with visual disturbances examined by Robertson¹⁰ (1944) atrophic retinitis, with accumulations of pigment in the choroid and optic neuritis were the changes most frequently found in the fundus These lesions were present in 4.9 and 2 per cent, respectively, of a series of 1,000 soldiers examined for some reason other than trauma in the ophthalmic clinic of an Army station hospital in the southwest Pacific in 1943 Malarial parasites

36 Wood, D J Accommodative Failure in Malaria and Influenza *Brit J Ophth* **4** 415, 1920 Robertson¹⁰

were present in the blood of 75 per cent of the men in the area. In a number of Robertson's patients who complained of sudden diminution of vision, atrophic retinitis or optic neuritis ultimately became apparent, although ophthalmoscopic examination disclosed no abnormalities at the onset of symptoms. In Talbot's observations on military personnel infected with malaria, optic neuritis was also noted as a cause of amblyopia, headache and a type of orbital pain that was made worse by pressure or movement of the eye.³⁷ The experience of these recent observers corresponds closely to that reported by many others in the past.³⁷ It is agreed by most authors that the optic neuritis of malaria is followed by atrophy in a relatively small proportion of cases when adequate antimalarial treatment is given.³⁸ Typical retrobulbar neuritis is less common than papillitis.³⁹ Opacities in the vitreous are rarely reported to be present with changes in the fundus associated with malaria, and iritis and cyclitis are seldom attributable to malaria except possibly for a mild iritis which occasionally accompanies herpetic keratitis. Similarly, cataract is a rare complication among the ocular disturbances of malaria.⁴⁰

In a consideration of visual disturbances in malaria, the possibility of toxic effects from quinine in therapeutic use must be ruled out. It has generally been held that the changes associated with toxic amblyopia or amaurosis due to quinine are sufficiently typical to be distinguished from malarial manifestations.¹⁶ Pamaquine naphthoate may also cause changes in vision, but this drug has been employed by so small a proportion of physicians reporting on ocular complications of malaria that there has been little opportunity for misinterpretation. With the current increased use of other antimalarial agents, such as quinacrine, which appear to be considerably less toxic to the eye, the possibility of confusion is, of course, reduced. An impression of a relatively low incidence of visual disturbances due to quinine itself is obtained when it is considered that although more than 200 cases of ocular manifestations have been reported in the one hundred years since the first observation of such a complication quinine has been one of the most widely used drugs during this period.⁴¹ Consistent with a low incidence is the report that,

although the use of quinine for malaria in the region of Memphis, Tenn., has been relatively common, no recent case of blindness due to quinine poisoning and only 2 cases of atrophy of the optic nerve produced by the drug were recognized among 30,000 new patients in the ophthalmic clinics of that city during a ten year period (1926-1936) and only 1 new case was recorded in the general hospitals of the same city during a five year period.⁴² Similar figures were reported by Manson⁴² (1920), who found only 2 cases of amaurosis due to quinine poisoning and none of amblyopia or atrophy of the optic nerve due to the drug among 12,000 patients treated for malaria in military service in World War I. However, blindness is at times produced by quinine and has been observed after both minute and massive doses. Interpretations of the ophthalmoscopic observations with regard to the mode of the toxic action of quinine have been the subject of considerable controversy centering on the question whether the effect of the drug on the retina is a result of ischemia due to alterations produced in the vessels or of a direct toxic action on the neural elements themselves. Without a detailed discussion of the evidence, it may be said that clinical, histologic and experimental observations have not yet been adequate to settle the question, but recent opinion seems to favor a direct action of quinine on neural elements of the retina as a primary factor.⁴³ Clinically, the onset of amaurosis is sudden and complete to the extent of loss of light perception. In most instances the pupils have been described as dilated and fixed. Examination of the fundus at first reveals only edema of the whole retina, with a red macula, but in the course of a week or two the disks become pale and the arteries may become greatly narrowed. During this period of apparent advance in the pathologic process of the fundus, vision often gradually returns. The coincidence of these phenomena has been referred to as the "paradox of quinine amaurosis."⁴⁴ In some cases, however, vascular and visual changes did not coincide, while in a few cases no arterial narrowing was observed.⁴⁵ In subsequent months

37 Woods, H. Optic Neuritis After Measles and Intermittent Fever, *Arch Ophth* **21** 95, 1892. MacNamara. Malarial Neuritis and Neuro-Retinitis, *Brit M J* **1** 540, 1890. Sulzer.²

38 Toulant.⁸ Kiep.¹⁶ Blatt.^{18a}

39 Villard.^{26a} Toulant.⁸

40 Blatt.^{18a} Dedimos.⁵

41 Richardson, S. The Toxic Effect of Quinine on the Eye, *South M J* **29** 1156, 1936.

42 Manson, W. H. Personal Experiences on the Ocular Sequelae of Malaria, *Glasgow M J* **93** 127, 1920.

43 McGregor, I. S., and Loewenstein, A. Quinine Blindness, *Lancet* **2** 566, 1944.

44 Duggan, J. N., and Nanavati, B. P. Quinine Amblyopia, *Brit J Ophth* **15** 160 and 164, 1931.

45 Perner, L., and Saskin, E. Toxic Amaurosis Due to Quinine Treatment with Sodium Nitrite Administered Intravenously, *J A M A* **119** 1175 (Aug 8) 1942. Ballantyne, A. J. Quinine Amaurosis with Report of a Case, *Brit J Ophth* **1** 153, 1917. Fox, L. W. Acute Uni-Ocular Neuritis, *Am J Ophth* **1** 113, 1884. Duggan and Nanavati.⁴⁴

central color scotomas may be present for a time, but progressive improvement in central vision is usually noted, almost always with persistent concentric constriction of the fields and hemeralopia. Characteristically, at the relatively late stage, the optic disks are white and the retinal vessels much reduced in diameter. In occasional cases loss of vision is permanent.⁴³ The clinical features of quinine poisoning thus differ in several respects from the changes attributed to malaria, especially with regard to the extent of the retinal edema and vascular alterations, as well as to the character of the visual loss.

The occurrence with malaria of neurologic disturbances other than those concerned with vision has been repeatedly described, both recently and in the past. Among soldiers hospitalized for malaria in World War II, "neuralgia" or hyperalgesia of various sensory nerves has been described as having a high incidence (18 per cent) by Harvey⁴⁶ (1944). In most cases the malaria was caused by *Plasmodium vivax*. The neurologic disturbances are explained by Harvey as probably due to transient lowering of the threshold of excitability of nerves which are subjected to asphyxia from partial blocking of their blood supply. The symptoms noted are pain or burning and tingling of varying duration in the distribution of a single cranial or peripheral nerve, occurring most commonly in the first week after the onset of active malaria, during or just prior to the first acute attack of fever. Symptoms also occur often, but with diminishing frequency, in subsequent attacks, as well as during latent periods. Numerous authors have noted the frequent occurrence with malaria of neuralgia of the trigeminal nerve, especially of the supra-orbital and infraorbital branches of the ophthalmic division.⁴⁷ This complication was observed by Griesinger⁴⁸ in 13 of 414 cases of malaria, while it was said to be one of the most frequent complications of benign tertian malaria by Toulant⁸ and of masked malaria by Bispham.¹¹² Most characteristically, pain, localized in the distribution of the supraorbital nerve, starts rapidly at the beginning of a chill and lasts from two to five hours. Often the pain is succeeded by hyperesthesia in the same location but may be recurrent with subsequent attacks of fever or be replaced with hypesthesia. Usually the neuralgia may be controlled by antimalarial treatment.⁸

46 Harvey, A. M. A Type of Neuritis Associated with Malarial Fever, *Bull Johns Hopkins Hosp* **75** 225, 1944.

47 Santos Fernandez, F., and Madan, D. Les hématozoaires de Laveran dans la névralgie ophtalmique, *Arch d'opht* **12** 266, 1892. Carlotti⁶ Kiep¹⁶.

48 Griesinger, cited by Toulant⁸.

The attack of hyperalgesia is often accompanied with conjunctival hyperemia, tearing and photophobia and may be followed by the appearance of herpetic keratitis with corneal hypesthesia. Consideration of the neurotropic characteristics of the herpes virus and the occurrence of herpetic lesions following other types of disturbances of the trigeminal nerve, such as those produced by operative procedures⁴⁹ or a toxic agent,⁵⁰ has suggested to some observers a possible causal relationship between the malarial trigeminal neuralgia and herpetic keratitis.^{18a}

Relatively infrequently, transient ocular motor disturbances, seldom with permanent paralysis,⁸ have been ascribed to malaria. Paresis of the abducens nerve has been noted more commonly than weakness of the other ocular muscles.⁵¹ Less often, facial paralysis with lagophthalmos has been reported.¹⁶ It has been suggested that the mechanism producing the paresis may be an injury of the motor nerves as a result of vascular changes. A similar mechanism has been postulated for motor disturbances of the extremities associated with malaria, which differ, however, in that they are characterized by increased muscular tone accompanied with hyperalgesia (Harvey,⁴⁶ 1944). It has been suggested by Blatt^{18a} (1928) that the ocular motor disturbances may be the result of central lesions, since their onset is often associated with headache and dizziness. Involvement of isolated muscles would be consistent with nuclear lesions, but the usual transitory nature of the paresis might be better explained by peripheral disturbances. Attempts to account for the muscular weakness on a toxic basis have not explained how isolated muscles may be involved without disturbances of the other muscles.

Besides the various ocular manifestations usually described, there are less well recognized changes which warrant brief mention. Among these are the "malarial vessels" of Goldfeder,⁵² which are described as large, superficial conjunctival vessels running horizontally without branching until they reach the limbus, and which Goldfeder claimed to be pathognomonic of malaria. Similar vessels have been observed in a

49 Richter, R. B. Observations Bearing on the Presence of Latent Herpes Simplex Virus in the Human Gasserian Ganglion, *J Nerv & Ment Dis* **99** 356, 1944.

50 Humphrey, J. H., and McClelland, M. Cranial Nerve Palsies with Herpes Following General Anesthesia, *Brit M J* **1** 315, 1944.

51 Blatt^{18a} Kirk²¹.

52 Goldfeder, A. E. Malaria und Auge. Ueber ein allgemein zugängliches Augensymptom der chronischen und larvierten Malaria, *Arch f Schiffs- u Tropen-Hyg* **40** 207, 1936.

large proportion of patients with malaria by Rozende,⁵³ Mufel⁵⁴ and Bushmich,³⁵ but these vessels were also found in patients with diseases other than malaria.³⁵ Goldfeder and associates⁵⁵ also described the occurrence of "blue stripes" in the fundus as a characteristic of malaria, but it is uncertain whether this lesion corresponds to changes described by other observers. Inequality of the pupils, attributed to unilateral irritation of the sympathetic nervous system, was observed by Dedimos⁵ in 25 per cent of malarial patients with moderate splenic enlargement, and this observation has not been seriously at variance with the reports of other authors.⁴⁵ An icteric tinge of the conjunctiva has often been described in cases of malaria, even of the masked type.⁵⁶ This discoloration is considered to be due to deposition of malarial pigment and is analogous to

the discoloration of the nerve head and retina observed with chronic malaria. There appears to be no characteristic conjunctivitis or scleritis associated with malaria.⁵⁷

In conclusion, it appears that malaria may be the inciter of several characteristic disturbances in various parts of the eye. The processes encountered are mostly monocular but moderately incapacitating, including the relatively frequent, though nonspecific, complication of herpetic keratitis and several of the disturbances which appear to be best explained on the basis of vascular lesions attributable to the malarial parasites. Lesions of the choroid, retina and optic nerve, which from histologic evidence appear to be due to emboli of parasitized cells and which are commonly bilateral, appear to be the most serious of the complications, because of their interference with vision. Treatment of these ocular disturbances with antimalarial drugs has in general been successful, except in case of the herpetic keratitis, caused by a virus, for which specific chemotherapy is lacking.

243 Charles Street

57 Dedimos⁵ Carlotti⁶

53 Rozende, C. Contributo brasileira ao signal ocular de Goldfeder, no diagnostico da malaria chronica e larvada, Cong argent de oftal (1936) 2 626, 1938

54 Mufel (1936), cited by Bushmich³⁵

55 Goldfeder, A. E., and Moldavskaja, V. D. Malaria and the Eye, Arch Ophth 17 228 (Feb) 1937

56 Fialho⁷ Talbot⁸ Manson⁴²

News and Notes

EDITED BY DR W L BENEDICT

GENERAL NEWS

Ophthalmologic Seminar, Emory University School of Medicine.—Emory University School of Medicine will hold an ophthalmologic seminar honoring the memory of Dr Abner Wellborn Calhoun on April 4 to 6, 1946. Guest lecturers will be Dr William Benedict, Dr John Dunnington, Dr Parker Heath, Dr Walter Lillie, Dr Derrick Vail and Dr Frank Walsh. All members of the ophthalmologic profession are cordially invited as guests of Emory University. Reservations at the Atlanta Biltmore Hotel should be made early.

The Scientific Exhibit, Ninety-Sixth Annual Session of the American Medical Association—Application blanks are now available for space in the Scientific Exhibit at the Ninety-Sixth Annual Session of the American Medical Association, to be held at San Francisco, July 1 to 5, 1946. Applications for space will close on February 25.

Requests may be sent either to Dr Georgiana Theobald, 120 Medical Arts Building, 715 Lake Street, Oak Park, Ill., who is the representative to the Scientific Exhibit from the Section on Ophthalmology, or to the Director, the Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10.

Refresher Course in Ophthalmology, Washington University School of Medicine—Washington University School of Medicine, in St

Louis, announces a four week intensive refresher course in ophthalmology from June 3 through June 29, 1946. The 131 hours of didactic lectures will cover the important phases of ophthalmology. The course is designed primarily for the returning veteran but should also serve as an excellent review for candidates for the examination by the American Board of Ophthalmology. Tuition fee \$200. An outline of the course, as well as more detailed information, will be sent on request. All applications or inquiries should be addressed to Dr Richard G. Scobee, director of graduate training in ophthalmology, Washington University School of Medicine, 640 South Kingshighway Boulevard, St. Louis 10.

UNIVERSITY NEWS

The William F. Norris and G. E. de Schweinitz Chair of Ophthalmology.—The William F. Norris and G. E. de Schweinitz Chair of Ophthalmology was established in the University of Pennsylvania on June 28, 1945, by a bequest under the will of Dr George E. de Schweinitz, professor of ophthalmology in the University of Pennsylvania School of Medicine from 1901 to 1924, and at one time a trustee of the university. The income of a fund of \$150,000 is available for the maintenance of the chair.

Dr Francis Heed Adler is the present incumbent of the chair.

Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

Anatomy and Embryology

ABERRANT OPTIC NERVE FIBRES FOUND BETWEEN RETINA AND HEXAGONAL CELLS
A LOEWENSTEIN, Brit J Ophth 29:180 (April) 1945

Two cases of aberrant nerve fibers of the optic nerve of different sizes are described. The first type was found in a case of pigmented tumor of the optic disk infiltrating the neighboring retina and choroid. The lesion is assumed to be a malignant degeneration of a pigmented nevus of the optic disk. This type involves maldevelopment of the posterior retinal layers in front of the growth. The second type was seen in a case of hypertensive retinopathy with edematous swelling of the papilla and a large druse. The nerve fiber tissue found between the retina and the pigmented epithelium was degenerated in a ganglioform manner. The retina in front of this tissue was well developed. A mechanical pushing out of the optic nerve fibers, due to the edema and the pressure of the druse, is assumed to be the cause.

The article is illustrated

W ZENTMAYER

Injuries

TRAUMATIC OCULAR INJURIES IN SOLDIERS
B RONES and H C WILDER, Am J Ophth 28:112 (Oct) 1945

This is a statistical study of 399 enucleated eyes received at the Army Institute of Pathology Analysis, interpretation and clinical correlation will be attempted in studies now under way. The authors call attention to the absence of sympathetic ophthalmia.

W S REESE

IMPROVED TREATMENT FOR CHEMICAL BURNS OF THE EYE
L W OAKS, Am J Ophth 28:370 (April) 1945

Oaks believes it likely that chemicals may enter the anterior chamber in burns of the eye. He believes that paracentesis of the cornea should be established as a standard procedure in every case of a moderate or severe burn of the cornea in which any destruction of tissue or haziness results, irrespective of the chemical involved.

W ZENTMAYER

INTRAOCULAR FOREIGN BODIES
W O LODGE, Brit J Ophth 29:205 (April) 1945

Lodge describes a technic for the localization of intraocular foreign bodies in cases in which

the vision of the injured eye is good but the foreign body is located too far forward to be seen with the ophthalmoscope.

An illustrative case is described

W ZENTMAYER

Lens

ELECTRICAL CATARACT NOTES ON A CASE AND A REVIEW OF THE LITERATURE
A L ADAM and M KLEIN, Brit J Ophth 29:169 (April) 1945

A man aged 51 came into contact with live electrical apparatus. A discharge at 11,000 volts passed by sparking contact with his metal-rimmed glasses and ear pieces. Second and third degree burns were present around the orbits and along the temples and the bridge of the nose. There were second and third degree burns of the upper part of the body. Visual symptoms developed six months after the accident when the sight began to fail. There was no pathologic change except in the lenses. Both lenses showed opacities, chiefly vacuoles in the anterior capsule and subcapsular grayish dots, in some places confluent. On the anterior capsule of the left lens was a seal-like gray opacity. Corrected vision was 6/12 in each eye, at the end of sixteen months the ocular condition remained unchanged.

A review of the literature shows that the number of cataracts due to contact with an electric current has increased recently, corresponding to the increase in the number of electrical accidents of all kinds. The onset of the ocular disturbance is usually delayed. There is not sufficient evidence to state the cause of this type of cataract or the process by which it develops.

As a practical suggestion, it is advisable that persons employed in electric power stations should not wear spectacle rims containing metal.

The article is illustrated

W ZENTMAYER

THE EFFECT OF ASCORBIC ACID ON THE OCCURRENCE OF HYPHEMIA AFTER CATARACT EXTRACTION
I MANN and A PIRIE, Brit J Ophth 29:175 (April) 1945

The results of all cataract operations in the hospital for 1942-1943, when ascorbic acid was not given, were compared with a similar series for 1943-1944, with the difference that in the second series an attempt was made to saturate every patient with ascorbic acid at the time of opera-

tion All other factors, such as surgeons, type of operation and diet in hospital, remained the same throughout the two years

The authors conclude that there is no evidence that the occurrence of hyphemia following cataract extraction is influenced by administration of ascorbic acid

W ZENTMAYER

Lids

ACQUIRED BLEPHAROPTOSIS E B SPAETH, Am J Ophth 28:1073 (Oct) 1945

A brief classification is presented for convenience in consideration of the various forms of acquired ptosis of the upper lid The surgical needs for the correction of these defects are varied and exacting Suggestions for the maximum correction of these dissimilar situations are presented since the procedures outlined have proved satisfactory in many instances Recognized indications demand varied methods of correction One surgical technic will best correct only one type of the condition Attention to this exacting situation should give excellent results, its neglect will bring disappointment

Spaeth presents a number of photographs and descriptions

W S REESE

Neurology

ELECTRICAL SENSITIVITY OF THE EYE IN SOME OPTIC-NERVE DISEASES RESULTING FROM CRANIO-CEREBRAL TRAUMATA S V. KRAV-KOV and A N MURSIN, Am J Ophth 28: 363 (April) 1945

Kravkov and Mursin feel that the electrical sensitivity of the eye might help in differentiating optic neuritis and choked disk, and from their investigations they conclude that determination of this factor is helpful and frequently reveals abnormalities when the ophthalmoscopic examination does not

W S. REESE

WERNICKE'S DISEASE (ENCEPHALITIS HEMORRHAGICA SUPERIORIS) D KRAVITZ and R H STOCKFISCH, Am J Ophth 28: 596 (June) 1945

Three cases of superior hemorrhagic encephalitis are reported in which there was no history of alcoholism but the condition was due to dietary deficiency

A complete cure was obtained in the second and third cases and an almost complete cure in the first case In case 1 the disease had been present for a much longer time, and the symptoms were much more severe and had reached the irreversible stage but, fortunately, to only a slight extent It is interesting to note that only in case 3 were other features of vitamin B deficiency present, namely, cheilosis and glossitis.

W S REESE

PHOTIC DRIVING A WALKER, J WOOLF, W HALSTEAD and T CASE, Arch. Neurol & Psychiat 52:117 (Aug) 1944

Early in the study of the electrical activity of the cerebral cortex Berger noted that a photic stimulus to the retina notably altered the spontaneous alpha rhythm This observation gave added impetus to the study of the phenomena associated with stimulation of the visual system, which led to the discovery of one of the most interesting methods of modulating the pattern of the occipital electroencephalogram, namely, that of intermittent photic stimulation of the retina, or "photic driving" The modifications of the normal cortical rhythms which may be produced by this method permit certain analyses of normal, and possibly pathologic, visual mechanisms

The authors found that intermittent photic stimulation of the retina of the cat, dog, monkey and man may modify the electroencephalogram from the occipital cortex to take on a frequency synchronous with that of the flicker The effect is augmented by increasing the intensity of the luminous flux, with a maximum at approximately 80 foot candles The driving is more pronounced when the photic stimulus is at the blue end of the spectrum than when it is at the red end The cortex of the macaque monkey may be made to follow a flicker with a frequency of 34 per second, but the optic nerve and the lateral geniculate body will follow frequencies of 62 and 59 cycles per second, respectively Lesions of the visual pathways impair photic driving

R IRVINE

WERNICKE'S DISEASE CLINICAL AND PATHOLOGIC STUDY OF 42 CASES H E RIGGS AND R S BOLES, Quart J Stud on Alcohol 5: 361 (Dec) 1944

Riggs and Boles present a study of 42 cases in which the diagnosis of Wernicke's disease (superior hemorrhagic polioencephalitis) was confirmed by necropsy A history suggesting chronic alcoholism was obtained in only 18 cases, while in all the cases there were either clinical signs of a deficiency state or, at necropsy, evidence of organic change which would contribute to the condition The diagnosis in these 42 cases was made almost invariably at necropsy on the basis of characteristic changes in the brain The clinical syndrome described by Wernicke was found to be of little value as a criterion of diagnosis Disturbance of psychic function was present in all cases, usually as an initiating symptom, and in 70 per cent it was associated with other signs of involvement of the nervous system The classic triad of clouding of consciousness, ophthalmoplegia and ataxia was not noted in its entirety in a single case The clinical and necropsy observations in 42 cases of Wernicke's disease suggest that in these cases nutritional

deficiency provided the essential background for the condition. Alcohol, although contributing to the deficiency state in at least 43 per cent of the series, was apparently not a primary factor in the genesis of the disease.

J A M A (W ZENTMAYER)

Ocular Muscles

CAUSES OF FAILURE IN THE TREATMENT OF SQUINT F D COSTENBADER, *Am J Ophth* 28: 1123 (Oct) 1945

After a somewhat brief reference to the literature, the pitfalls in the treatment of squint are listed and discussed. The commonest and most important factors in failure to correct the defect would seem to be (1) persisting amblyopia, due to belated, inconstant or insufficient occlusion, (2) failure to recognize or sufficiently to treat suppression and/or abnormal retinal correspondence, (3) difficulty in managing a combined vertical and lateral imbalance, (4) failure to distinguish between the accommodative and the mechanical elements in a given case of squint, and (5) failure to stabilize and obtain functional cure by adequate postoperative orthoptic training.

W S REESE

AN ANALYSIS OF ONE HUNDRED CASES OF STRABISMUS TREATED ORTHOPTICALLY R U GILLAN, *Brit J Ophth* 29: 420 (Aug) 1945

The purpose of the survey was a desire to ascertain at first hand the effects of orthoptic treatment in developing (1) orthopsis and (2) stereopsis.

Analysis of 63 cases in which orthoptic treatment only was given revealed that in 36 cases the eyes became straight, or nearly straight, and good stereoscopic vision developed. The conclusion is reached that a prerequisite to successful treatment by orthoptic means only is the existence of simultaneous perception and fusion and strabismus of not more than 25 degrees, preferably much less, viz. about 10 degrees.

Analysis of 37 cases in which combined orthoptic treatment and operation was employed showed that the eyes became straight, or nearly straight, in 23 cases and good or fair stereoscopic vision developed in 17 cases. The conclusion is reached that good stereoscopic vision is an important factor in maintaining orthopsis even when operation has been performed.

An analysis is made of a control series of 50 cases in which the patients were under observation for an average of nine months and had no treatment except the prescription of glasses. In none of these cases did orthopsis or stereoscopic vision develop.

An analysis is made of the results of refraction in the 100 cases under review and of the effects

of correction with glasses at the commencement of orthoptic treatment. In only 3 cases were the eyes straight at the beginning of treatment, in 25 cases there was reduction of squint, and in 44 cases there was no change in the degree of squint. The conclusion is reached that the lower degrees of squint are most likely to be corrected with glasses but that an essential condition of this eventuality is the preexistence of simultaneous perception and fusion and a capacity for development of good stereoscopic vision, that not even under such conditions do all eyes become straight but that with the addition of orthoptic treatment they are very likely to do so.

In the light of these results, the possible cause of strabismus is discussed, and the conclusion is reached that the absence or failure of stereoscopic vision is the main etiologic factor in the production of concomitant strabismus.

Some objections to this theory are discussed, but they are not thought to invalidate it.

W ZENTMAYER

Orbit, Eyeball and Accessory Sinuses

ACTINOMYCOSIS OF THE ORBIT E CHAN, *Chinese M J* 63: 98 (Jan) 1945

A Chinese merchant aged 58 had a history of a nodule developing in the right lower lid for five years. There was an ulcerating mass adherent to the inferior orbital margin with a sinus leading into the orbit, which discharged a grayish yellow fluid. The discharge contained knots of myceliums with radially projecting tips—actinomycetes. Tissue from the mass was made up of inflammatory and epithelioid cells and many giant cells of the foreign body and Langerhans type.

W ZENTMAYER

Parasites

THELAZIASIS OF THE CONJUNCTIVA S C LIANG, *Chinese M J* 63: 70 (Jan) 1945

A case of infection of the conjunctiva with *Thelazia callipeda* is reported from Kweiyang, Kweichow. Unlike previously reported cases, there was no complaint of subjective symptoms in the infected eye. The parasites were accidentally discovered during routine examination. Thelaziasis, like other parasitic diseases, produces eosinocytosis. The source of infection in this case was probably dogs or cats.

W ZENTMAYER

Physiologic Optics

DIRECT UTILIZATION OF THE EYE AS A CAMERA W A MANN, *Am J Ophth* 28: 451 (May) 1945

Mann describes experiments on animal eyes demonstrating that the eye can be used as a camera by putting a film behind an optical glass placed over a window cut in the region of the

macula, the glass being of a curvature approximating the posterior conformity of the globe.

W S REESE

Retina and Optic Nerve

DRUSEN (HYALINE BODIES OF THE OPTIC DISK)
H P WAGENER, Am J M Sc 210:262
(Aug) 1945

Wagener makes a critical review of the literature of drusen and gives the results of electroencephalographic studies on 6 patients with drusen in the optic disks. The results are interesting though probably not clinically significant. The records of 2 patients were essentially normal, the electroencephalogram of 1 patient showed slight delta activity in the right temporal area. A third patient, who presented a post-traumatic syndrome resulting from a head injury, had a record of low potential but otherwise normal. The record of the fourth patient showed some dysrhythmia, that of the fifth patient, dysrhythmia and bilateral occipital delta activity, grade 1 and 2, and that of the sixth patient, generalized dysrhythmia. All the patients except the sixth had normal roentgenograms of the head. In the sixth patient the sella was enlarged and the dorsum eroded. One of the patients presented Adie's syndrome, 1 had syphilis of the central nervous system, and the sixth had, with emotional instability, signs of an organic cerebral disorder, mainly in the cerebellum.

Although it cannot be considered definitely proved at present that drusen of the optic disk are really slow-growing astroblastomas of hereditary and familial occurrence and that they represent a variant of tuberous sclerosis, the evidence presented is at least suggestive and intriguing and warrants further study and investigation.

W ZENTMAYER.

CHANGES AT THE MACULA DUE TO SOLAR RADIATION C McCULLOCH, Am J Ophth 28:1115 (Oct) 1945

Seven cases of residual change at the macula probably due to solar radiation are reported. A method for plotting very small central scotomas with the tangent screen and a method for noting the properties of the normal macular reflex are described.

A small central scotoma was found in 6 of the 7 cases. The fundi in all 7 cases showed an abnormal yellow spot at the macula, surrounded by a dark ring. In 6 of the 7 cases the lesion was in the right eye. In 4 of these 6 cases the right eye was dominant, in 1 case the left eye was dominant, and in 1 case the dominance was not recorded.

In the discussion, it is pointed out (1) that other causes for cyst at the macula must be considered and the condition differentiated from

tobacco-alcohol amblyopia, colloid excrescences and the areas of suppression seen in scotometric examinations, and (2) that the pathologic change at the macula probably centers at the level of the pigment epithelium and not at the level of the retina.

W S REESE

Uvea

ANGIOID STREAKS OF THE DEEP LAYERS OF THE RETINA A J BEDELL, Am J Ophth 28:601 (June) 1945

Bedell records observations made on angioid streaks during the past several years, with special reference to the study of 4 cases. One of the patients was under observation for a short time, the second for four years, the third for eight years and the fourth for fourteen years. The author states that the narrow circumpapillary atrophy as such has nothing to do with the streaks and that, furthermore, when degenerative lesions of the macula develop they follow the usual clinical course of deep retinal or superficial choroidal hemorrhages, with exudate, edema and an expanding ring of blood. After many months, recurring hemorrhages stop, the exudate becomes organized, and the scar persists throughout life. This is not conceived to be an integral part of angioid streaks. The author does not believe that the ruptures on Bruch's membrane and the accompanying pseudo xanthoma elasticum are part of the same process, certainly not in all cases.

The article is illustrated.

W ZENTMAYER

DIABETIC IRIDOPATHY C A CLAPP, Am J Ophth 28:617 (June) 1945

Clapp reports 2 cases of this condition.

The term iridopathy is to be used when there occur changes in the iris which are of metabolic, not inflammatory, origin.

Diabetes may cause changes in the iris which may be confused with malignant melanoma.

Clinical and pathologic observations have apparently been confirmed by animal experimentation.

A further study of these changes is desirable, especially to ascertain whether they are limited chiefly to the diabetic patient, and to determine the cause.

W S REESE

Sympathetic Ophthalmia

SYMPATHETIC OPHTHALMIA FOLLOWING SUBCONJUNCTIVAL RUPTURE OF THE EYEBALL C A PERERA, Am J Ophth 28:581 (June) 1945

Perera reviews sympathetic ophthalmia, especially that following subconjunctival rupture of the globe. He reports a case of the latter and con-

cludes that allergy to uveal tissue plays an etiologic role in the production of sympathetic ophthalmia

W S REESE

Therapeutics

THE EFFECT OF DETERGENT ON THE PENETRATION OF SODIUM SULPHACETAMIDE (ALBUCID SOLUBLE) INTO OCULAR TISSUES M GINSBURG and J M ROBSON, Brit J Ophth 29 185 (April) 1945

The penetration of sodium sulfacetamide into the ocular tissues was studied both in living rabbits and in isolated ocular tissues. The application of the drug with a wetting agent, Duponol

ME dry, increases the penetration of sodium sulfacetamide into and through the cornea. Removal of the corneal epithelium results in a great increase in the penetration of the sulfonamide drug into and through the cornea, that is, the epithelium acts as a barrier to the passage of the drug. The wetting agent does not increase the passage of the drug into the denuded cornea (i.e., the cornea with the epithelium removed). It may be concluded that the wetting agent acts by overcoming the epithelial barrier. The results suggest that addition of a wetting agent to sodium sulfacetamide is of most value with infections of the cornea and iris.

W ZENTMAYER

Society Transactions

EDITED BY W L BENEDICT

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Regular Meeting, Nov 19, 1945

Present Status of Radiation Therapy of Ocular Diseases. DR HAYES MARTIN

Dr Martin discussed the forms of radiation therapy which have been used at the Memorial Hospital in the treatment of lesions about the eye. These consist of roentgen radiation, the unfiltered radon bulb and radon gold seeds. He pointed out that filtered radium applicators should never be used about the eye because of the impossibility of providing adequate protective shielding with the applicator. He discussed the various complications and untoward sequelae of radiation therapy about the eye and pointed out that many of these complications can be avoided by use of the proper technic, others, although not completely preventable, are often justifiably incurred provided that the disease for which the treatment is given is more serious than the complication. Radiation therapy about the eye is indicated for only a limited number of malignant tumors, benign neoplasms and diseases. He briefly discussed the technics of irradiation and the dosage and showed a number of illustrative cases.

Exophthalmos Caused by Eosinophilic Granuloma of Bone. DR MAYNARD WHEELER

Eosinophilic granuloma of bone was first recognized as a distinct entity in 1940. At least

37 cases have now been reported, but in only 1 was exophthalmos present. The tumor occurs as a rapidly developing, painful swelling over the skull, a rib or a long bone in a child or a young adult. Multiple lesions are frequently shown roentgenographically. The diagnosis is made by the finding on histologic examination of large numbers of histiocytes, many giving evidence of phagocytic activity, and occasional large multinuclear giant cells, numerous eosinophilic and neutrophilic leukocytes, and many clumps of mononuclear eosinophilic cells.

A typical case was reported in a man aged 34 who complained of exophthalmos with pain of five weeks' duration. The lesion was curetted, with recovery. This favorable result has been reported in all cases whether excision, curettage or roentgen irradiation was employed.

Dermatomyositis with Retinopathy. DR JACK V LISMAN

This paper will be published in full, with discussion, in a future issue of the ARCHIVES.

Uses of Air in Ophthalmology. DR WENDELL L HUGHES, Hempstead, N Y

This paper will be published in full, with discussion, in a future issue of the ARCHIVES.

Ocular Changes Associated with the Blood Dyscrasias. DR ISAAC S TASSMAN, Philadelphia (by invitation)

This paper will be published in full, with discussion, in a future issue of the ARCHIVES.

Book Reviews

New Goals for Old Age Edited by George Lawton, D Sc Price, \$2.75 Pp 210 New York Columbia University Press

Much water has flowed under the bridges of social and cultural theory since a famous physician notified all and sundry, in a more or less strabismic world, that every man of 40 was not, as Stevenson claimed, either a physician or a fool but definitely *passé* for effective thought or activity. Today one notes as an indication of progressive civilization a similarly advancing preoccupation with the physical and spiritual problems of the very young and the very old. *Les extrêmes se touchent* in a way which probably did not occur to the French commentator, and infancy as well as senility—*sit venia verbo*—especially the latter, is of interest to a large reading public of laymen, as well as physicians.

It was Stevenson, again, who said "Age cannot bring, it must find, the philosophic mind," and those who seek for this *primum desiderium*, a consummation devoutly to be wished, will find much of interest in this symposium, with a wealth of information from practical experience and wide study, as well as humor and wit. The editor contributes largely to this harvest in his prologue to what he calls a conspiratorial collection of papers. These, numbering nearly a score, range over the broad field of physical, mental and spiritual reactions of presenescence. The result is an authoritatively presented, and often interestingly embellished, panorama. There are chapters on "Adjustment over the Life Span", "Aging Mental Abilities, and Their Preservation", "The Older Person in the Family, in the Changing Social Scene and in the World", "Physical Changes in Old Age and Their Effects on Mental Attitudes", "Occupational Therapy", "The Creative Urge in Older People", "Mental Diseases of the Aged," and an especially stimu-

lating contribution by Alice I. Bryan, of Columbia University, School of Library Service "Toward a Science of Bibliotherapy." This volume certainly invites one into one of the highways and byways of medicine, if not of ophthalmology, and as such will no doubt be favorably received.

An extensive bibliography and a detailed index add to its value.

PERCY FRIDENBERG

Le penicilina y sus aplicaciones en oftalmología
By Antonio Ros, M.D. Price, \$3 Pp 123
"México, D.F. S.A. Bajel, 1945"

This small book cites the importance of this new drug in clinical work and then gives a short and rather fanciful sketch of Alexander Fleming's early life.

There follows an account of his discovery and the application of the drug, its effects, toxicity and dosage. Its applications in ophthalmology are reported, and the author's method, preferably by intramuscular injection, is submitted, he preferring that means to use of collyriums or ointments and reporting cases thus cured. He concludes that the drug is a prophylactic against ocular infection before operations.

The author recommends in 2 cc the intramuscular injection of 20,000 units every three hours. The remedy has been tried by the author in treatment of various infections and of conditions in which the cause was obscure. He thinks that the treatment is particularly of value before operations, when he recommends that five injections be given, one at the time of operation and the others directly after. This remedy, in the author's opinion, is superior to the sulfonamide drugs. A bibliography is appended.

J. I. MIDDLETON

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are devoted to clinical work

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A BASKET TYPE IMPLANT FOR USE AFTER ENUCLEATION

LIEUTENANT COLONEL NORMAN L. CUTLER
MEDICAL CORPS, ARMY OF THE UNITED STATES

THIS is a preliminary report on a new type of implant for use in enucleation procedures. It is designed to impart more rapid movement to the prosthesis and to reduce the possibility of postoperative complications.

The history of evisceration and enucleation has recently been reviewed by Dimitry.¹ Although there are surgeons who still do not use an implant of some form, either in the sclera or in Tenon's capsule, the majority today consider that a more adequately filled socket and a better functioning stump are obtained with an implant. Here there is diversity of opinion as to the material, the shape and the method of implantation.

It is a common observation that whether an evisceration or an enucleation with implantation has been done there is fairly good movement of the stump. This is true whether the rectus muscles have been sutured together or not. In fact, often surprisingly good movement in the socket is obtained with a simple enucleation. The problem has been to transmit the movement to the prosthesis. Its solution has been aided by the recent development of molded plastic artificial eyes, which give a better contact with the socket, resulting in increased movement.

It was with the idea of providing the socket with a better grip on the prosthesis that a new type of basket implant was devised to be placed in Tenon's capsule. This basket implant has been in routine use for several months in an Army general hospital designated as an eye center. During that time 50 enucleations have been done by eight different ophthalmologists using this type of implant. A study has been made of the size and shape of the basket, the operative procedure and the final prosthesis. Although this work is being continued and extended it is felt that sufficient standardization has been attained that a preliminary report may be made.

The purpose of a basket implant, with a resulting depressed area in the socket, is to give the prosthesis which has a stud projecting pos-

¹ Dimitry, T. J., The Socket After Enucleation and the Artificial Eye, Arch Ophth 31:18 (Jan) 1944.

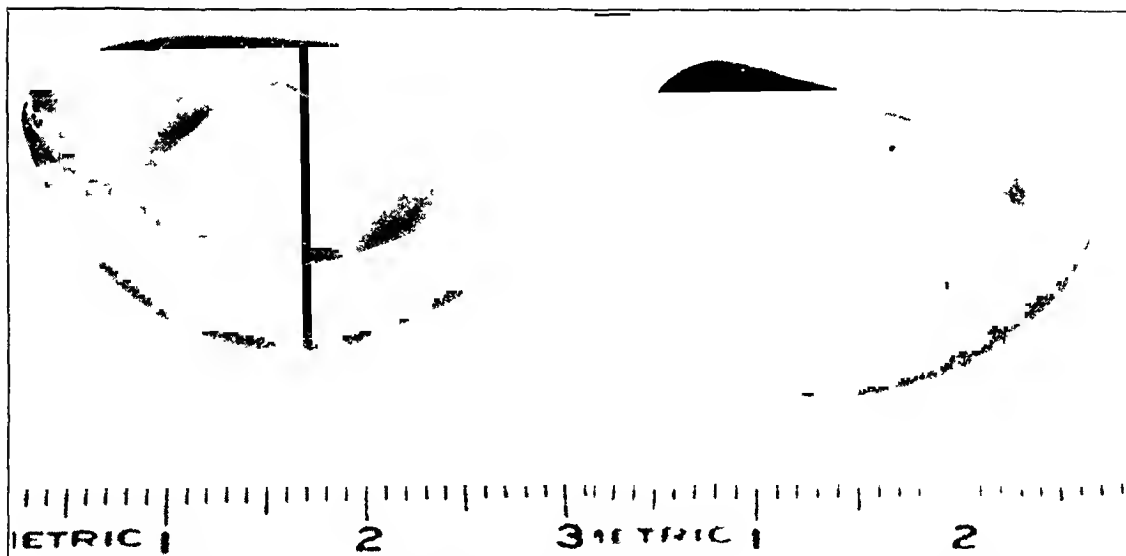


Fig 1—Plastic prosthesis, showing projecting stud on the posterior surface

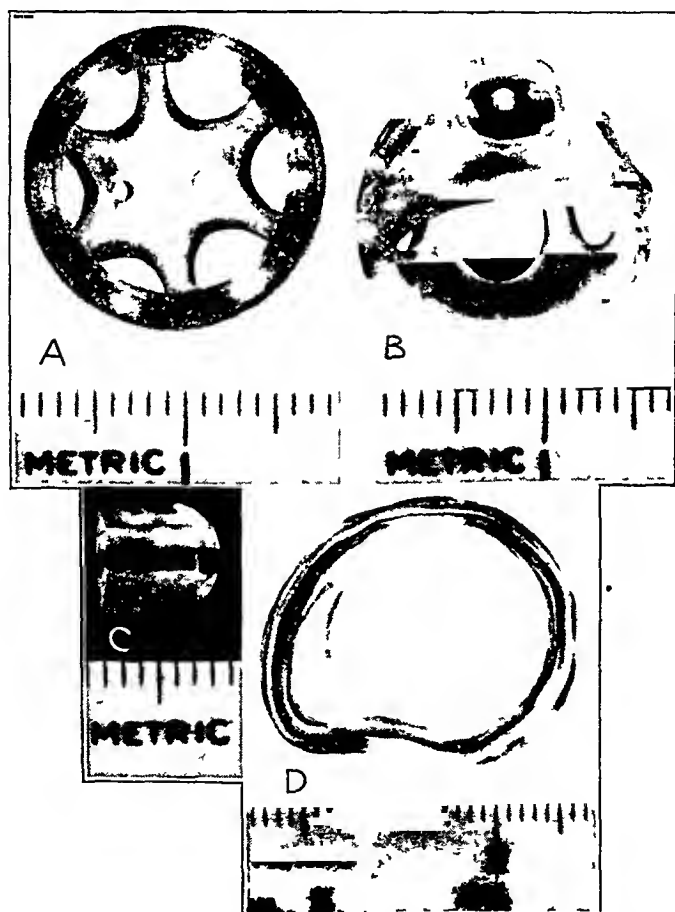


Fig 2—*A*, view of Lucite basket from above, *B*, lateral view of the basket, *C*, Lucite stud, and *D*, posterior view of Lucite basket with central depression for stud

teriorly (fig 1), a grip on the stump. This necessitates, of course, a custom-designed prosthesis and, in addition, imposes new problems of design on the artificial eye maker. This is due to the fact that there is more ability of the cuplike depression to move the artificial eye than there is space in which the eye can move. Thus, it is necessary to adjust carefully the size and shape of the prosthesis in order to use the minimum amount of space and still maintain a normal fissure. This is facilitated if no attempt is made to fill out a depressed upper lid with the prosthesis, but that is left to the surgeon.

The standard basket now used is shown in figure 2 *A* and *B*. It is made of Lucite (methyl methacrylate) and measures 11 by 15 mm. This size seems to be the best whether the eye to be enucleated is large or small. The anterior edge is slightly thickened. As shown in figure 2 *A* and *B*, the sides of the basket are fenestrated to allow for invasion of tissue. In addition, there are three holes in the bottom, measuring 1 mm in diameter, two of which are for sutures. Larger and smaller baskets have been tried, but a tendency to reduce movement has resulted in either case. Other materials are being tried, but Lucite has been found satisfactory up to the present time. The situation after several years will still have to be determined. A Lucite button, measuring 5 by 8 mm, with four 0.8 mm holes (fig 2 *C*) is used to tie the sutures through and maintain the depression during healing. Three double-armed sutures are used: black 0 nylon, blue 00 dermal and purple coarse dermal. These are used because of their greater strength and smoothness, allowing sutures to be pulled up without breaking. They are of different colors to permit ready identification. One inch (2.5 cm) straight intestinal needles are used to allow their passage through the plastic button.

At the end of the operation a special plastic retainer (fig 2 *D*) is placed inside the lids after the method of Gifford². This greatly reduces postoperative edema, keeps the basket centered and completely prevents any prolapse of the conjunctiva. The average operating time for this procedure is the same as for any implantation procedure, namely, twenty-two to twenty-five minutes.

Two baskets slightly smaller than the standard have been placed inside the sclera after evisceration. No advantage accrued as far as movement of the stump was concerned, and the depression into which the stud of the prosthesis fits was considerably smaller. In addition, there was extreme postoperative edema, involving the entire side of the face, which lasted seven to ten days. I have seen 2 cases in which a ball implant was placed in the sclera with extremely good movement, prac-

2 Gifford, S. R. Plastic Shell for Use in Simple Enucleation of Globe, *Arch. Ophth.* 30:775 (Dec.) 1944.

tically as good as that of the normal eye, but because of the smooth contour only a small amount could be transmitted to the prosthesis

Many enucleation procedures and implants have been devised to insure action of the ocular muscles, by suturing them in front of the prosthesis or to the prosthesis itself. It is my opinion, as previously stated that the problem of motion of the prosthesis does not lie in this solution. In fact, in the procedure to be described, no attention is paid to attachment of muscles at all. Figure 3 shows the posterior view of a basket implant removed at autopsy eight and one-



Fig 3—Posterior view of basket implant removed at autopsy eight months after implantation, showing muscles attached to the anterior edge

half months after operation from a patient who was killed in an automobile accident. It will be seen that all the muscles, including the oblique, are attached at or near the rim of the basket.

OPERATIVE PROCEDURE

Anesthesia is induced by intravenous injection of sodium pentothal and retrobulbar injection of 2 cc of 2 per cent procaine hydrochloride.

The eye is prepared in the usual manner. A speculum (Weeks) is inserted, the conjunctiva dissected from the limbus and the dissection

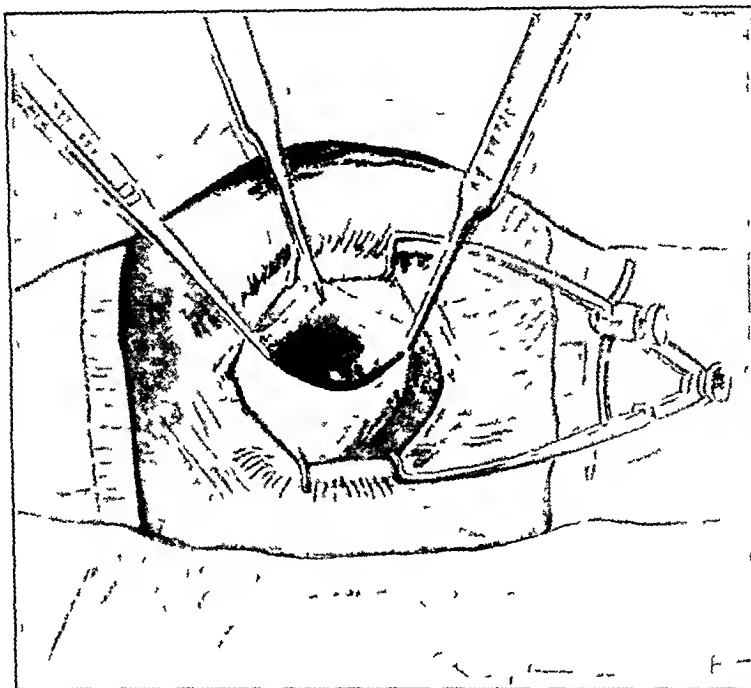


Fig 4—Tenon's space exposed, ready for insertion of the basket implant

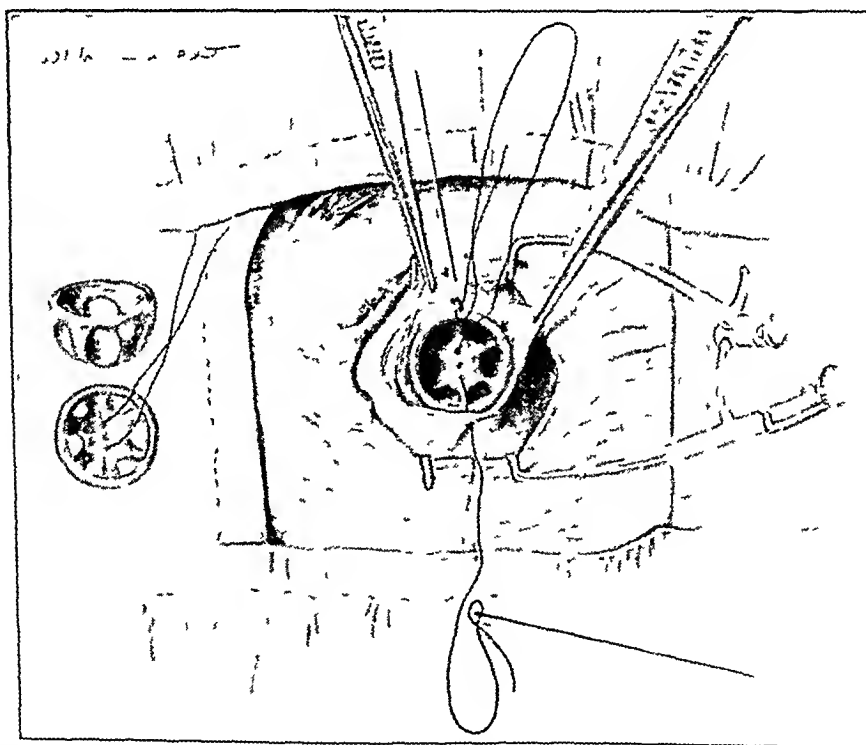


Fig 5—Basket with black 0 nylon suture inserted. The suture is carried through Tenon's capsule and the conjunctiva at 12 and 6 o'clock

carried to the foinices in all directions. The rectus muscles are then isolated and cut free from their insertions. The conjunctival opening usually is enlarged nasally and temporally about 2 mm to permit passage of the globe. The globe is grasped with fixation forceps at the tendon

of the internal rectus muscle and the nerve cut with enucleation scissors. The prolapsed globe is then freed from the oblique muscles and removed.

A dry gauze sponge and a little pressure usually reduce the bleeding quickly to enable one to inspect Tenon's capsule (fig 4).

The basket, with one black nylon suture, size 0, fitted with two straight 1 inch intestinal needles, is then placed in Tenon's capsule (fig 5). The upper suture is brought through a firm bite of Tenon's

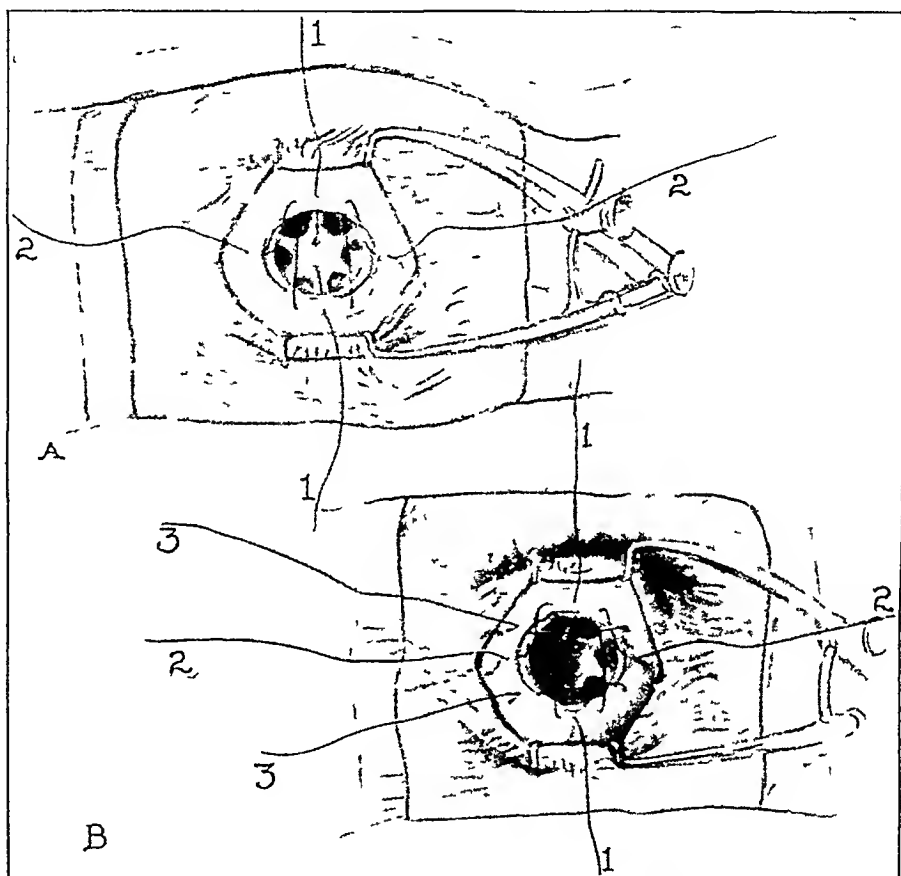


Fig 6—*A*, blue dermal mattress suture (2) carried through Tenon's capsule and the conjunctiva on either side of black nylon suture from within outward and, finally, through Tenon's capsule and the conjunctiva at 3 and 6 o'clock.

B, purple dermal mattress suture (3) carried from within outward through Tenon's capsule and the conjunctiva on either side of blue dermal suture (2).

capsule at 12 o'clock and out through the margin of the conjunctiva. The lower suture is brought out similarly at 6 o'clock.

A blue 00 dermal, double-armed suture with a 1 inch intestinal needle is then carried through Tenon's capsule and the conjunctiva about 2 mm on either side of the black suture which was placed at 6 o'clock (fig 6*A*). Each suture is then carried through in a similar manner at 12 o'clock. The suture on the right side is now carried through Tenon's

capsule and the conjunctiva at 3 o'clock on the same side, and the suture on the left, at 9 o'clock

A purple dermal (coarse), double-armed suture, similar to the blue dermal suture, is now placed about 2 mm on either side of the blue suture at 3 o'clock, the needle taking similar bites of Tenon's capsule and coming out through the conjunctiva. These two sutures are now

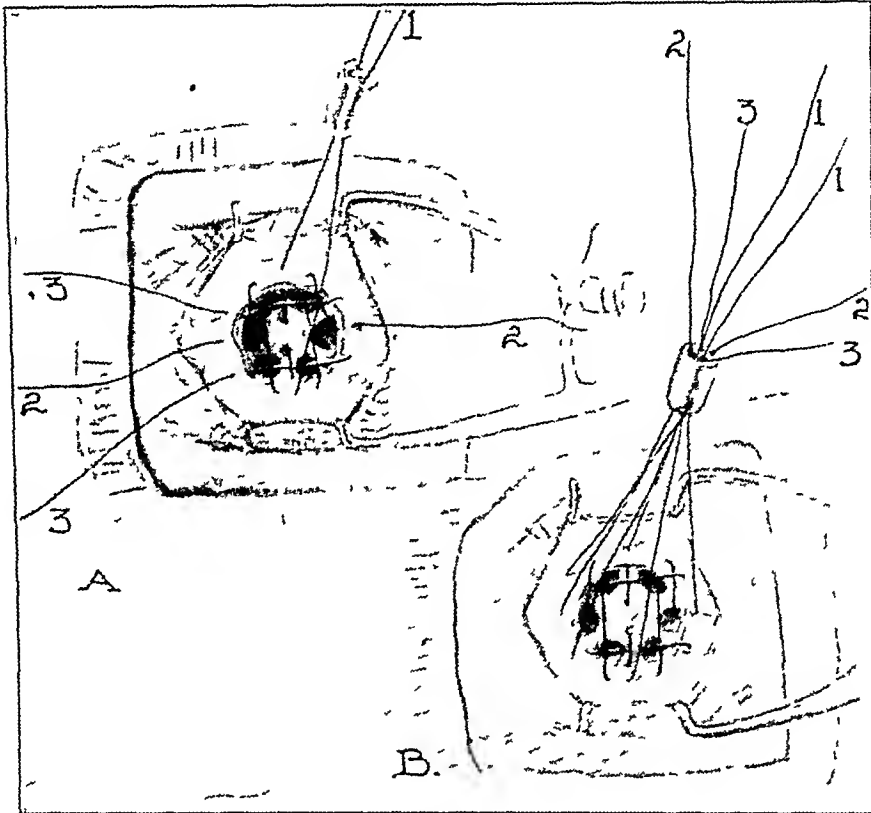


Fig 7—Black nylon suture (1) carried through holes in the Lucite stud B, purple dermal suture (3) carried through the same holes in the stud as suture 1, blue dermal suture (2) carried through the other two holes in the Lucite button

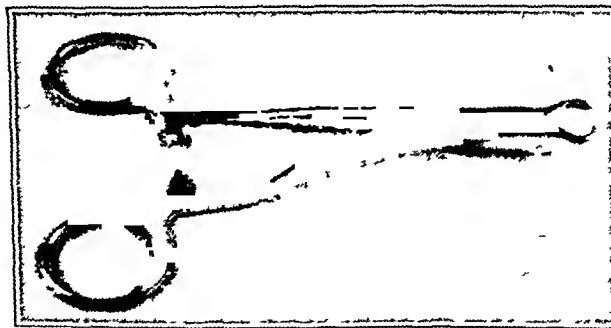


Fig 8—Button holder

carried across above all other sutures and brought out 2 mm on either side of the blue suture at 9 o'clock (fig 2 B)

These two mattress sutures (blue and purple) are placed as outlined in the preceding paragraphs, so that when they are pulled up they cause

a double imbrication, or folding, of Tenon's capsule and the conjunctiva and the black sutures still come out through the upper layer after this has been done. All sutures are carried through the Lucite stud, as shown in figure 7 *A* and *B*. Sutures 1 and 3 pass through the same two holes and suture 2 through the other two holes.

While the assistant holds the button with the lower end at the level of the rim of the cups with the button holder (fig 8), the blue suture is pulled up, tied and cut (fig 9 *A*), and then the purple suture is simi-

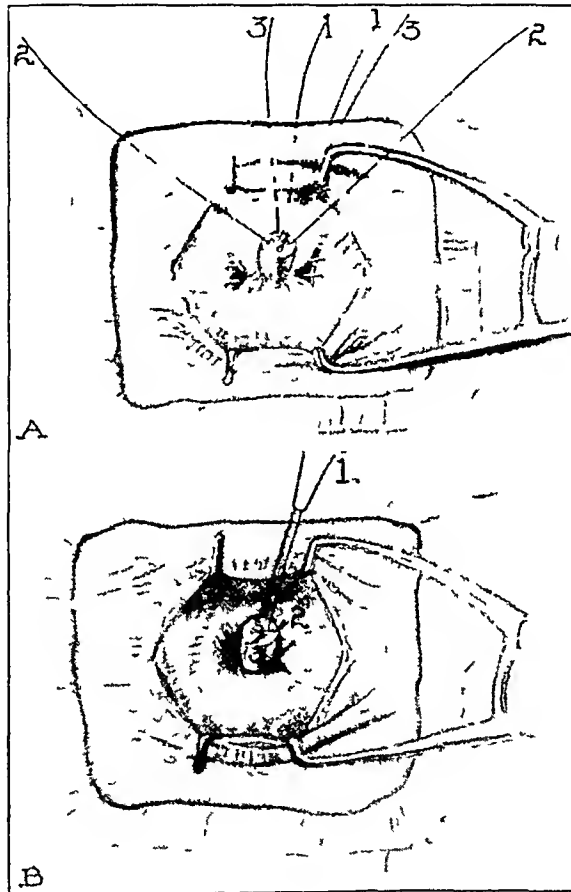


Fig 9—*A*, suture (2) pulled up, imbricating Tenon's capsule and the conjunctiva vertically

B, suture 2 tied and cut, suture 3 pulled up tight and cut through, imbricating Tenon's capsule and the conjunctiva horizontally and closing the basket opening

larly handled. This pulls Tenon's capsule and the conjunctiva into place and closes the opening.

A single tie is now placed in the black suture, and as this tie is gradually pulled up the index fingers make traction and a little pressure. The assistant then releases the button from the forceps. As this tie is pulled tight, it forces the button with Tenon's capsule and the conjunctiva down

into the cup. Three knots are placed and the suture cut (fig 10). No conjunctival sutures are necessary.

A Lucite retainer is placed inside the lids. An adhesive dressing with firm pressure but with no roller bandage is applied.

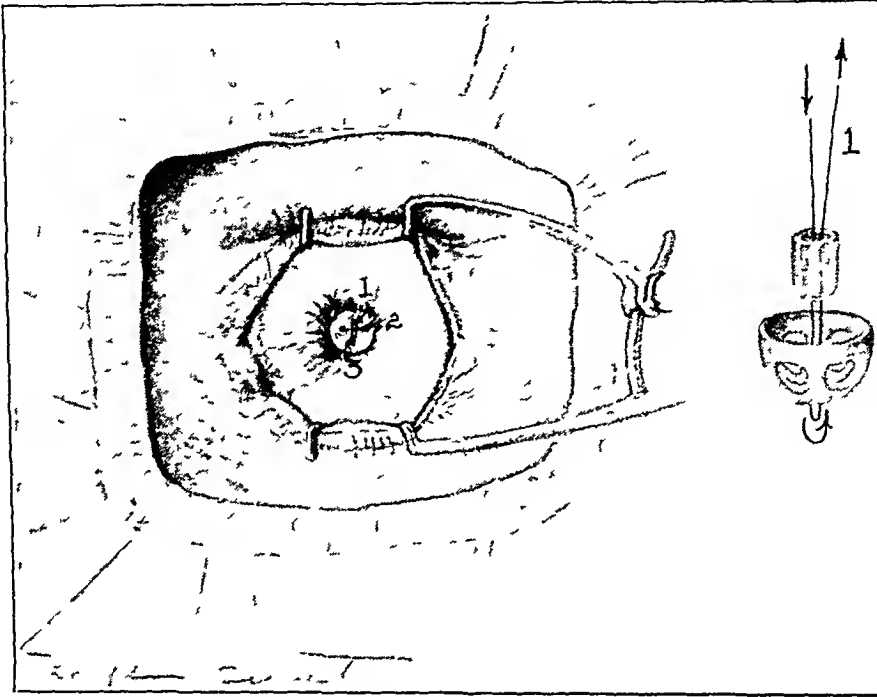


Fig 10—Suture (1) pulled up, tied and cut, forcing button with Tenon's capsule and conjunctiva down into the basket.

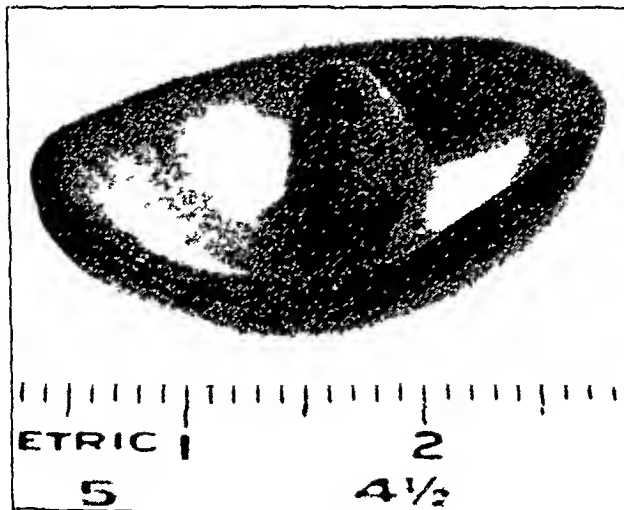


Fig 11—Plastic retainer

POSTOPERATIVE COURSE

The first dressing is done on the third postoperative day, the retainer being removed and the socket irrigated. The retainer is replaced, and if

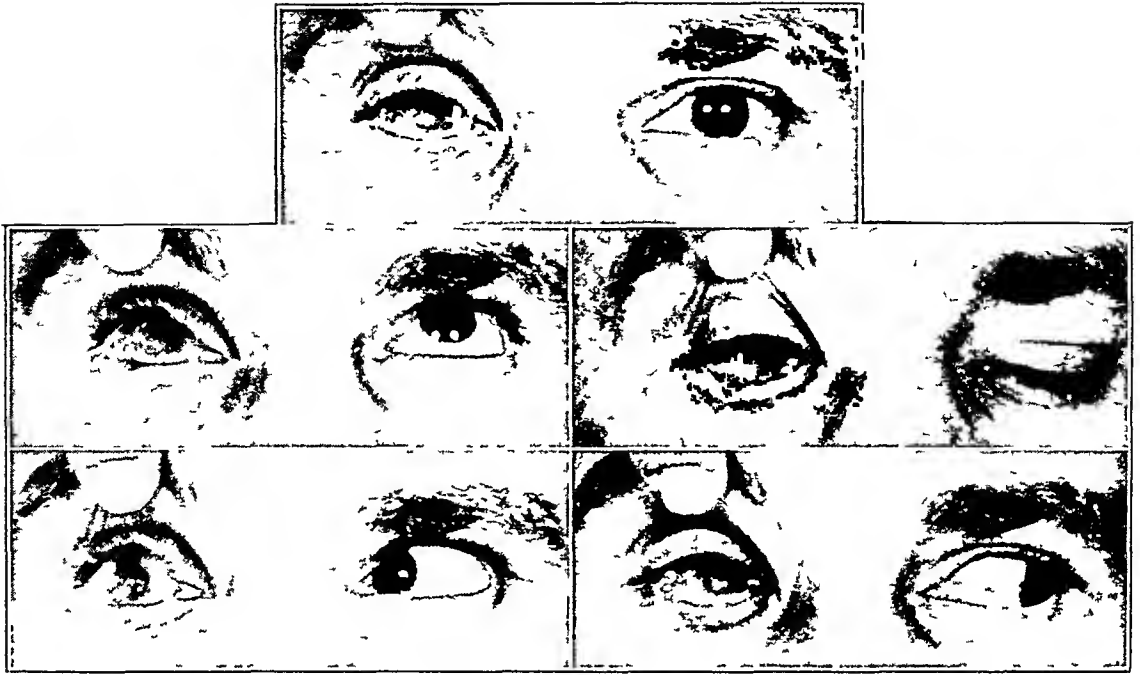


Fig 12—Appearance of the socket one month after operation, showing impression in the basket and the range of motion

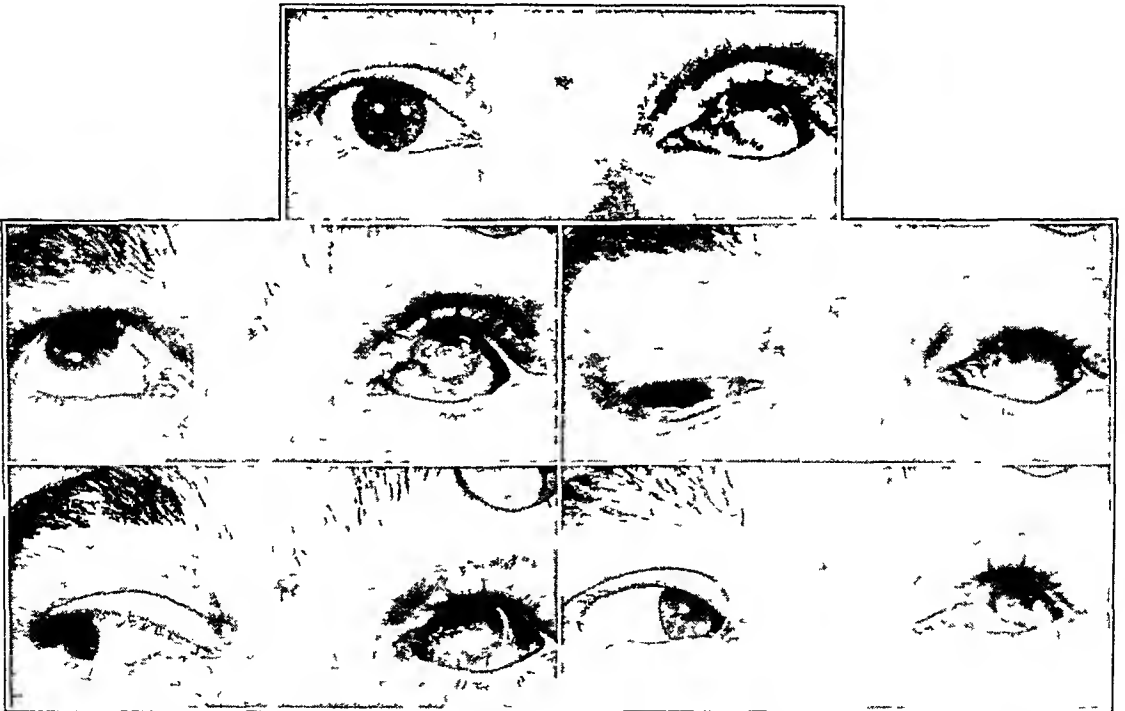


Fig 13—Appearance five months after operation, showing depression and movement of the socket

there is still some edema an adhesive dressing is put back on for two more days. In most cases the dressing can be omitted. On the fifth postoperative day the sutures and the button are removed. A temporary retainer with button attached (fig 11) is placed in the socket at this time. This is removed daily, and the socket is irrigated for a week.

In none of the cases in which operation was performed has there been any prolapse of the conjunctiva. This is probably due to the type of operation and to the retainer. In general, there has been little reaction and no discomfort at all after the first postoperative day.

At the end of two to three weeks, depending on the shrinkage of its tissues, the socket is ready for a custom-made prosthesis, similar to the one shown in figure 1.

COMPLICATIONS

It is important not to pull the sutures beyond the snug state, as otherwise pressure necrosis and exposure of the bottom of the basket will result. This complication will also occur if the button is not removed at the end of five days. If exposure of the bottom of the basket does occur, a retainer without a button attached is put in, and granulation and epithelization will take place in a few days, without impairment of the result. If, after the sutures and the button are removed on the fifth postoperative day, there is a thin-appearing lining on the bottom of the basket, a plain retainer can be used from one to three days and then a button retainer employed.

A sufficiently firm bite of Tenon's capsule must be obtained in placing the mattress sutures, since there is slight tension on the capsule when it is inverted into the basket. In 2 cases in which a ball implant was removed and a basket put in the sutures did not hold. This was also true in a case in which a considerable amount of scar tissue was present—the sutures cut through the inelastic scar tissue. It was necessary in these 3 cases to remove the baskets.

Postoperative hemorrhage has never been a problem in our cases. In the 3 cases just mentioned, in which the sutures did not hold because of scar tissue and the basket was removed approximately ten days after operation, it had to be dissected out. Certainly, the basket cannot be extruded.

PROSTHESIS

The socket is ready for the final prosthesis at the end of two or three weeks. This has been of plastic, made according to the standard Army procedure and under the direction of Capt Stanley F Erpf and Capt Arthur L Lundblad of the Dental Corps of the Army of the United States.

The prosthesis is not made from an impression of the socket, since that would result in its occupying too much of the available space. Figure

1 shows some variations in the prostheses that have been fitted. In general, the stud is adjusted to fit into the depression, and the base around this stud is cut away to allow the edge of the basket to come forward when the socket is turned. Through support of the stud, there is considerable relief of pressure on the tissues in the region of the fornices.

It is not absolutely necessary to use a custom-made eye with a stud, good movement can often be obtained with a Snellen form. The reason for this is that the movement of the prosthesis is in part due to the change in the shape of the socket when the basket rotates, one side becomes shallow and the opposite side deep, and the eye has to move.

The following tabulations were made on the basis of observations on 60 sockets fitted with artificial eyes. Practically all of them were fitted with custom-made plastic eyes. It is realized that this small number may not represent a true cross section. The series was collected from the wards without regard to the preoperative condition. It consisted of 20 sockets without implants, 20 with ball implants and the first 20 with basket implants.

Average Motion Degrees	No Implant	Ball Implant	Basket Implant
Nasally	19	19	28
Temporally	13	15	22
Superiorly	25	20	29
Inferiorly	12	20	30
Total	69	74	109

The sockets without implants showed the greatest variation in movement from patient to patient and those with basket implants the least variation. This is illustrated by the following tabulation.

Prostheses Having	No Implant	Ball Implant	Basket Implant
45° total horizontal movement	1 of 20	3 of 20	18 of 20
50° total vertical movement	6 of 20	8 of 20	19 of 20

It is felt that with more study of the most desirable shape for the prostheses, the statistics on the results of basket implantation will be further improved. These tabulations do not indicate the action of the oblique muscles, which is a prominent feature of the basket sockets. Neither do they indicate the most important characteristic of all, that is, the much more rapid response to movement of the muscle cone, with a notable decrease in the time lag as compared with that for the normal eye. The movement with this method comes more nearly within the average range of normal action than that with any previous procedure.

SUMMARY

On the basis of 50 operative procedures, a new type of basket implant for use after enucleation is presented which, with a new type of pros-

thesis, gives more instantaneous movement and a wider range of action. This procedure, combined with use of a plastic retainer, eliminates prolapse of the implant and shortens the period of postoperative convalescence.

Mr. Ralph Sweet contributed the drawings, Capt. Stanley Erpf, D. C., and Capt. Arthur L. Lundblad, D. C., A. U. S., modified and adapted the plastic prosthesis, and Corporal Cheetham, dental technician, helped in developing a technic for making the baskets.

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UVEAL BLASTOMYCOSIS

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MY interest in blastomycosis of the eye was incited by a patient who recently came under my observation. A review of the ophthalmic literature reveals only a meager contribution to the subject of fungous disease of the eye. Aspergillosis has been reported as penetrating the eye from a necrotic ulcer. Actinomycosis has occasionally been reported as an intraocular infection, and experimental metastatic infection of the eye has been demonstrated after intravenous injection of fungus in animals.¹ From this evidence, and from a few case reports not cited here, one may conclude that metastatic uveitis in association with systemic blastomycosis is not as unusual as it seems.

The name "blastomycosis" has often been declared a misnomer. The confusion results from the discrepancy between the American interpretation and the broader classification of a group of closely related diseases caused by yeastlike, or budding, fungi. The North American disease is a special type, known as "Gilchrist's disease." Cultural studies of North American and South American blastomycosis² show that the fungi in the two diseases are sufficiently similar to be placed in the same genus—*Blastomyces*. Paracoccidioidal granuloma, or South American blastomycosis, is caused by one species, the *Blastomyces brasiliensis*, while *Blastomyces dermatitidis* is the etiologic agent in North American blastomycosis.

In 1898 Gilchrist and Stokes³ described pseudo lupus vulgaris caused by a yeastlike organism which was nonfermenting and produced myceliums on artificial culture mediums. He called this causative fungus *Blastomyces dermatitidis*. The disease since then has often been called Gilchrist's disease, or blastomycosis. The organism is an oval, refractile body with thick walls and a double-contoured capsule.

In 1928 Castellani⁴ pointed out that blastomycosis included all conditions caused by a yeastlike, or budding, fungus but that in the United

1 Duke-Elder, W. S. Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2367.

2 Howell, A., Jr., and Conant, N. F. Similarity of Fungi Causing South American Blastomycosis (Paracoccidioidal Granuloma) and North American Blastomycosis (Gilchrist's Disease), *J. Invest. Dermat.* **5** 353 (Dec.) 1942.

3 Gilchrist, T. C., and Stokes, W. R. A Case of Pseudo Lupus Vulgaris Caused by a Blastomyces, *J. Exper. Med.* **3** 53, 1898.

4 Castellani, A. Blastomycosis and Some Other Conditions Due to Yeast-like Fungi (Budding Fungi), *Am. J. Trop. Med.* **8** 379 (Sept.) 1928.

States the term is used to denote a clinical entity characterized by the presence of granulomatous, verrucoid lesions in which fungi of the blastomycete type are found. Henrici⁵ called the fungus in blastomycosis "Cryptococcus gilchristi," under the genus *Oidium* oidiomycosis. Jacobson,⁶ in describing the mycology of Gilchrist's disease, stated that the causative agent is an encapsulated and budding organism represented by two species, *Blastomyces immitis* and *B. dermatitidis*, prevalent in and around Chicago. It grows widely and is found on vegetables of all sorts and on decaying wood. The organism is a budding yeast cell found in pus or in biopsy tissue after fixation. It is seen best unstained. Strong⁷ pointed out that the organism is 7 to 20 microns in diameter, is encapsulated by a thick, highly refractile membrane, forms myceliums in culture and buds in tissue.

Stober,⁸ in discussing the sources of infection, said that growth could be obtained on sterile moist bread, paper, cardboard, cotton, sawdust, fruit and vegetables. He had found the mold in damp wood in houses of patients with blastomycosis and cited scratch or injury from barbed wire while walking barefoot as a possible source of infection. Jacobson⁶ stated that blastomycosis is a protean disease in its clinical manifestations. No organ in the body is immune. There are two types of blastomycosis, cutaneous and systemic. The systemic disease affects every organ in the body—skin, lungs, kidneys, spleen, bones, prostate gland and meninges, in about that order of incidence. The skin is often the focus from which it reaches the lungs, through the blood stream. The onset is often insidious, starting as a papilloulcerative, verrucous, papillomatous or gummatous lesion of the skin, which persists for years, resulting in subacute or chronic pyemia. The infection results in malaise, loss of weight and strength, emaciation, recurrent chills, night sweats and irregular fever. Involvement of the lungs, with single or multiple pulmonary abscesses, often occurs. The diagnosis depends on finding the causative organism, in pus, in the secretions or in fixed biopsy tissue. The differential diagnosis must exclude tuberculosis, coccidioidal granuloma, syphilis sporotrichosis and bromide or iodine rash. The pathologic picture is similar to that of tuberculosis, with giant cells, except that the double-contoured bodies of blastomycosis are found in the tissue sections. The systemic type terminates fatally in 90 per cent of cases, and the

5 Henrici, A. T. *Molds, Yeast and Actinomycoses*, New York, John Wiley & Sons, Inc., 1930.

6 Jacobson, H. P. *Fungous Diseases*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

7 Strong, R. P. *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, Philadelphia, The Blakiston Company, 1942.

8 Stober, A. M. Systemic Blastomycosis. A Report of Its Pathological, Bacteriological and Clinical Features, *Arch. Int. Med.* **13**: 509 (April) 1914.

disease lasts from three weeks to three years. The treatment is symptomatic, together with rest, good food and administration of vitamins and potassium iodide.

Reports of fungous infection of the eye are relatively uncommon, especially intraocular infection. Blastomycosis of the eye has been reported in a few instances. Ball⁹ illustrates a case of blastomycotic dermatitis involving the eyelids. In most cases of blastomycosis involving the eyes there has been a direct extension from the conjunctiva or the lids. In 1 such case, reported by Ferguson,¹⁰ a tubercle-like growth on the conjunctiva developed from a beefy-looking growth on the cheek. McKee¹¹ reported a case of blastomycosis destroying the lids and producing ulcers of both corneas. It had also spread from the cheek and did not become intraocular. Wilson¹² described a case of conjunctival blastomycosis which developed from the scratch of a fowl. The antecedent history of injury followed a week later by the appearance of the lesion is a valuable point with respect to the incubation period.

Churchill and Stober¹³ recovered a pure culture of blastomycetes from the vitreous of an eye of a patient who had systemic blastomycosis. A description of the ocular lesion was not given except that the eye was affected by the disease. Schwartz¹⁴ gave the only pathologic report of an eye infected with blastomycosis that I have been able to find in the literature. In the autopsy report lesions of the skin, subcutaneous tissue, lungs, spleen, knee joint and eye are mentioned. The ophthalmic report was as follows:

The cornea was thickened and showed a perforation near the limbus. The anterior chamber and iris angle were almost entirely obliterated by an exudate of polymorphonuclear leukocytes, blastomycetes and giant cells. In the central portion of the iris was a medium sized area of necrosis.

The organisms were of variable sizes, having a highly refractile, double-contoured capsule, surrounding a granular or dark staining mass.

REPORT OF A CASE

W. M., a white man aged 64, a night watchman, was first admitted to the hospital in July 1942, with polyarthritis of six months' duration. The cutaneous

9 Ball, J. M. *Modern Ophthalmology*, Philadelphia, F. A. Davis Company, 1927, p. 272.

10 Ferguson, A. S. *Blastomycoses of Eye and Face Secondary to Lung Infection*, *Brit. M. J.* **1**: 442 (March 17) 1928.

11 McKee, S. H. *Blastomycoses of the Cornea*, *Internat. Clin.* **3**: 50 (Sept) 1926.

12 Wilson, R. P. *Blastomycoses of the Conjunctiva*, *Bull. Ophth. Soc. Egypt* **28**: 99, 1936.

13 Churchill, T., and Stober, A. M. *A Case of Systemic Blastomycoses*, *Arch. Int. Med.* **13**: 568 (April) 1914.

14 Schwartz, V. J. *Intraocular Blastomycoses*, *Arch. Ophth.* **5**: 581 (April) 1931.

lesions were of six weeks' standing, but the history was not accurate. The left elbow, left ankle and right knee joint were swollen and painful. He had a generalized papular disease of the skin, with some pustules covered with large scabs. The right pupil was sluggish and small. The temperature varied from 99 to 100 F almost every afternoon but was normal in the morning. The urine showed a 1 plus reaction for albumin, a 1 plus reaction for pus and a rare hyaline cast. Examination of the blood revealed 3,800,000 red cells and 13,300 white cells per cubic millimeter, 70 per cent hemoglobin, 76 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 2 per cent eosinophils and 7 per cent monocytes. His stay in the hospital was one week at this time.



Fig 1—Discoid, discrete, scaly, elevated lesions of the skin of the right arm and forearm and the right side of the trunk

He was readmitted to the hospital on Sept 20, 1942, with severe pain in his right eye. He still had the skin disease and the polyarthritic symptoms, in addition, he was mentally confused, disoriented, emaciated and dehydrated. The cutaneous lesions were discoid and measured 0.5 to 2 cm in diameter, they were distributed over the nose, cheeks, lobes of the ears, neck, hands, forearms, trunk, legs and ankles. Over the trunk the lesions were in various stages of evolution, healing with violaceous, atrophic scars (figs 1 and 2). There were red, tender, swollen abscesses on the left elbow, the left ankle and the right

knee joint The temperature, usually 99 to 100 F, occasionally reached 101 F The urine showed a trace of albumin, and the pus cell content was graded 2 plus The blood count revealed 5,000,000 red cells and 22,100 white cells per cubic millimeter, 77 per cent hemoglobin, 80 per cent polymorphonuclear leukocytes, 13 per cent lymphocytes and 7 per cent monocytes The reaction to the Mazzini test was negative A Mantoux test gave a negative reaction to tuberculin in 1:1,000 dilution The spinal fluid was clear and colorless, with no cells The total protein was 27 mg per hundred cubic centimeters, the Kolmer reaction was negative and the colloidal gold curve was 1122200000 Biopsy of



Fig 2—Discrete, disk-shaped, pink lesions of the skin with scaly, elevated border Some are covered with brown crusts

the skin showed that the epidermis was the site of pronounced hyperplasia, confined more or less to the pigment cell layer There were a superficial down-growth of rete pegs and moderate edema of the squamous epithelium Beneath the epithelium in the upper papillary portion of the corium was a heavy infiltration of polymorphonuclear leukocytes and epithelioid cells, all of which tissue was edematous Scattered through this cellular infiltrate were numerous giant cells in which double, refractile, yeastlike bodies were seen They were thought to be the so-called *Blastomyces hominis*, typical of blastomycosis of the skin

A culture of material from the cutaneous lesions of blastomycosis yielded a growth of a fungus identified as *Candida parapsilosis*

Roentgenograms of the right knee, tibia and fibula and the right side of the skull revealed irregular areas of destruction without reaction of the bone around the lesions. There was destruction of the lower third of the patella (fig 3)

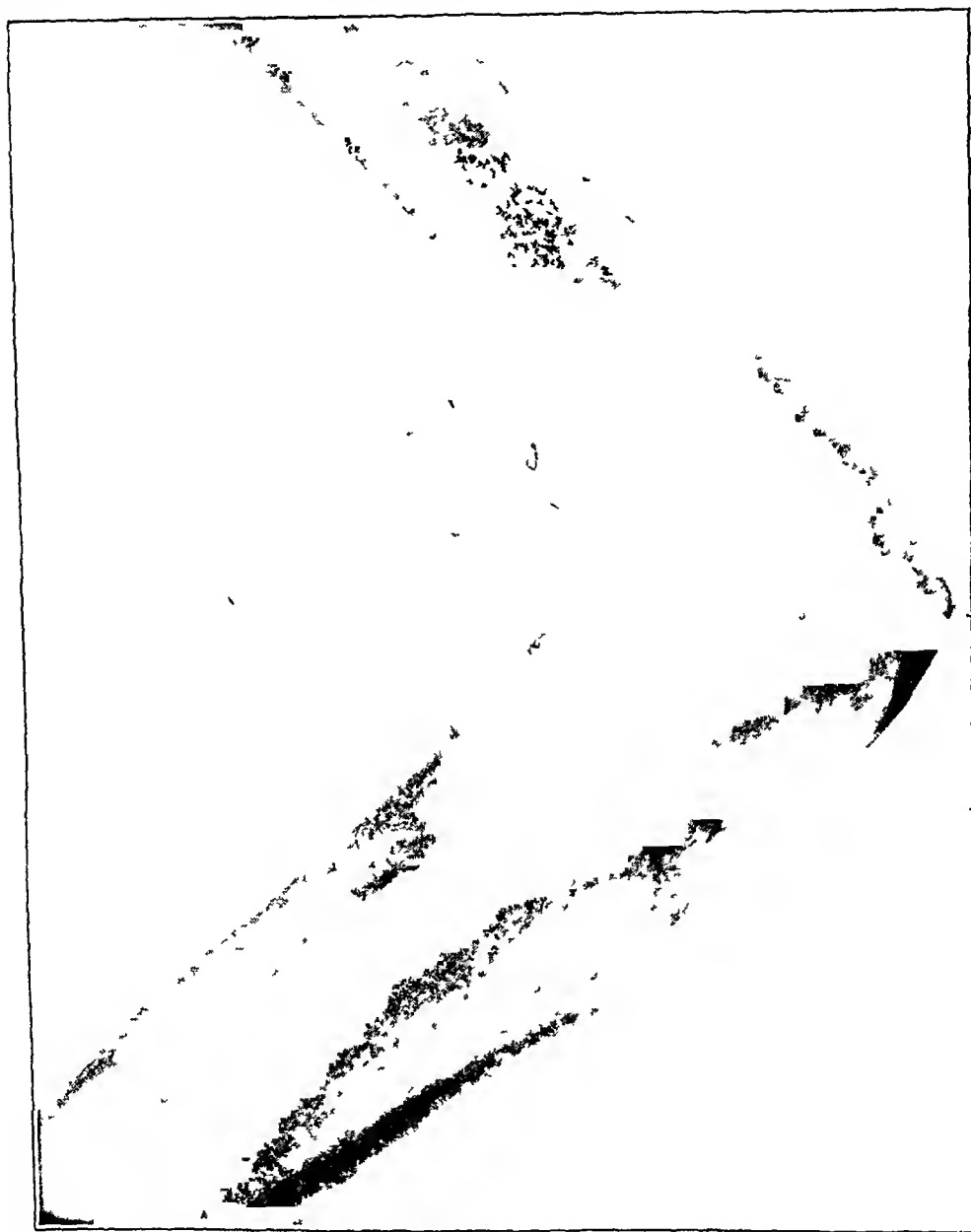


Fig 3—Roentgenogram of the right knee, showing irregular areas of destruction without reaction of the bone. The lower third of the patella is destroyed.

The tibial lesions (fig 4) were mainly confined to the cortex in its middle and lower thirds. The lower end of the femur showed subcortical involvement. The skull had two areas of destruction in the right parietal bone. Irregular scattered areas of consolidation in both lungs, with linear bands extending outward from the hilus, were seen in the roentgenogram of the chest. It was the conclusion of the roentgenologist that the appearance and location of the lesions in the bone, together with the type of lesion in the lungs favored a diagnosis of blastomycosis.



Fig 4—Cortical lesions of the tibia in its middle third



Fig 5—Injection of the ciliary body of the right eye The pupil was small and fixed, with posterior synechias A yellow nodule occurred at the free border of the iris, and a yellow growth extended into the angle of the chamber from 4 to 6 o'clock



Fig 6—Section representing 14 mm of lung Double-contoured, yeastlike blastomycetes occur in the cytoplasm of the endothelial cells

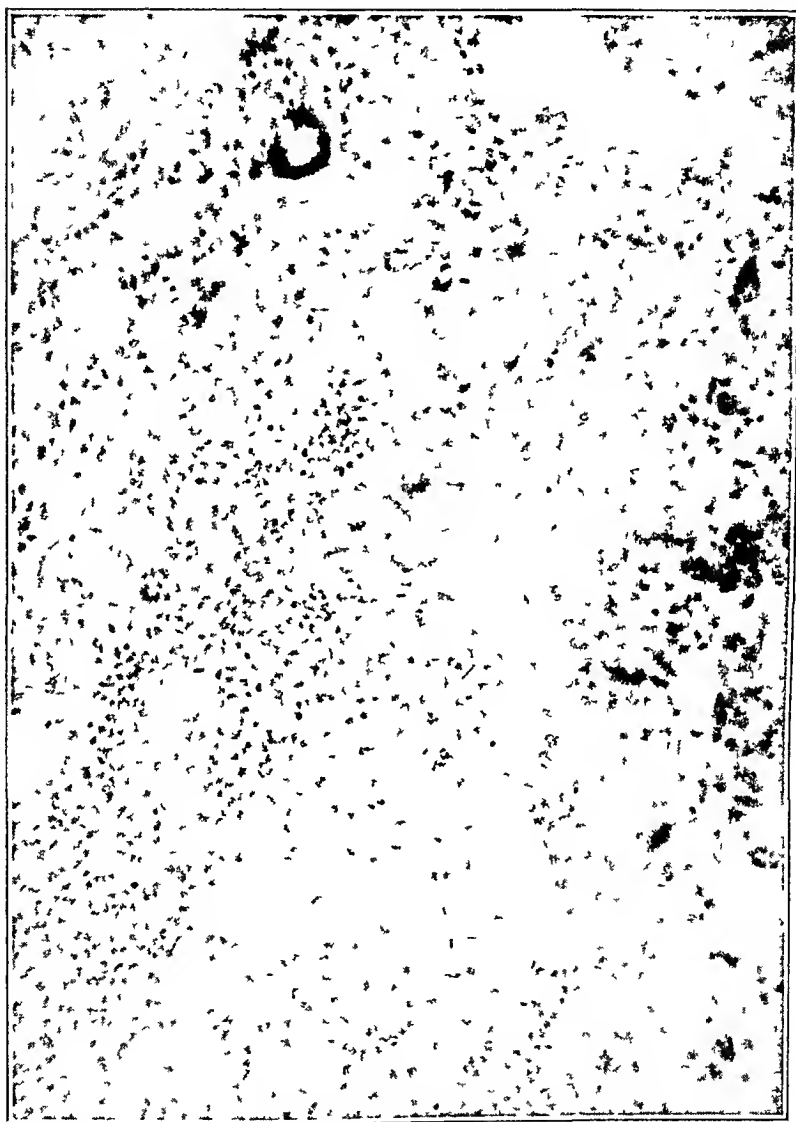


Fig 7—Section representing 25 mm of the prostate gland, showing the granulomatous type of necrosis

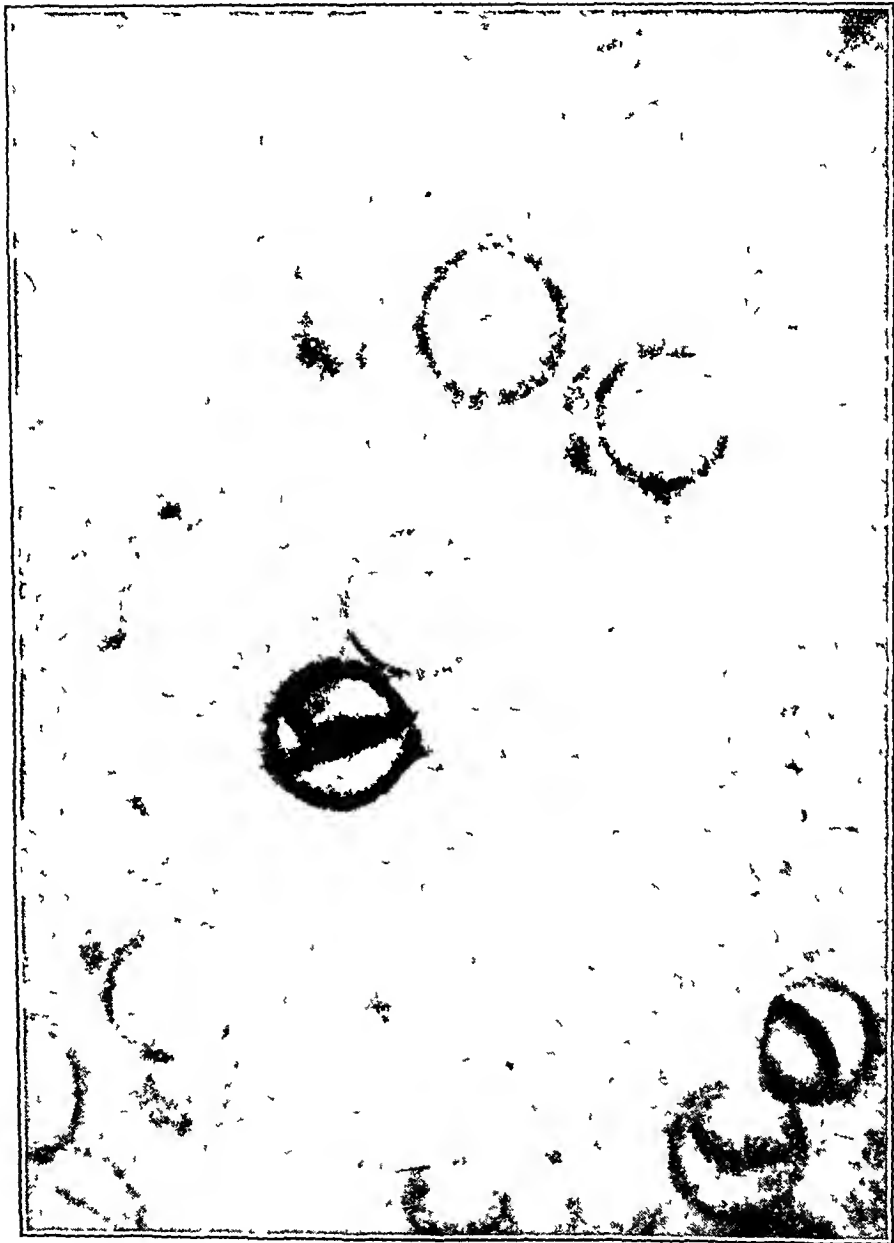


Fig 8—Section of the prostate gland seen with the oil immersion lens. Double-contoured bodies of the yeast cell are shown

The patient had severe photophobia, moderate injection of the ciliary body of the right eye, a total posterior synechia and a small, fixed pupil. At 8 o'clock on the free margin of the iris was a yellowish, tubercle-like nodule. Extending into the angle of the anterior chamber at the limbus was another yellow, tubercle-like lesion, apparently protruding through the iris at its base (fig 5). Paracentesis of the anterior chamber and examination of the aqueous for blastomycetes gave negative results, but the plasmoid intraocular fluid was not aspirated.

The patient's condition continued to have a downhill course, and he died on Dec 7, 1942.

Autopsy—The conspicuous lesions on postmortem examination were multiple nodular areas scattered throughout both lungs. Microscopic examination of these

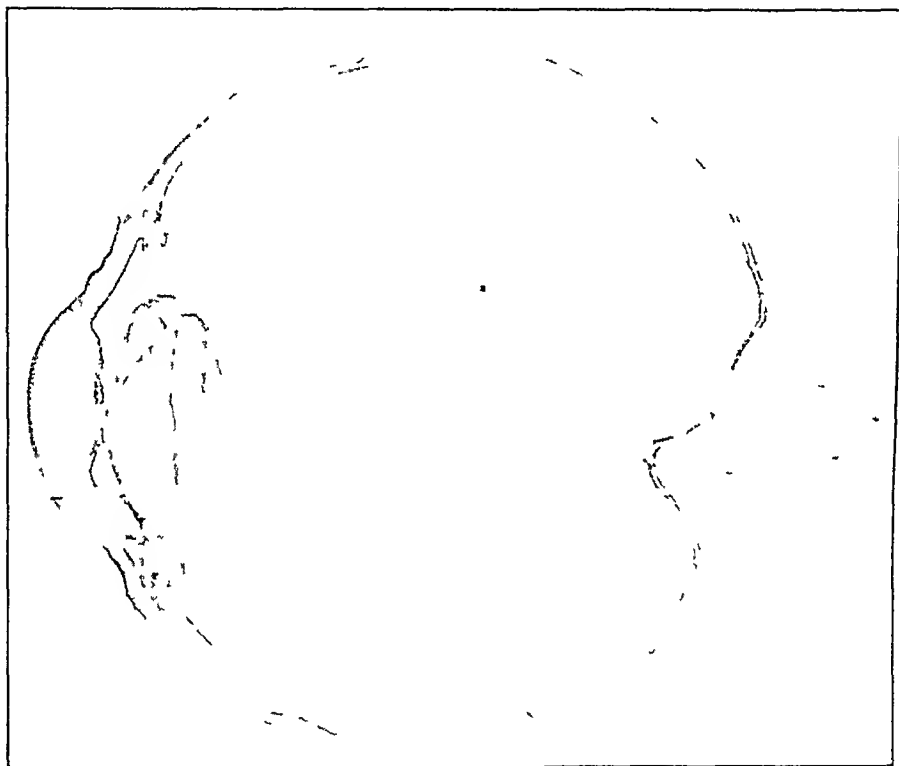


Fig 9—Inflammatory mass involving the root of the iris and the ciliary processes, occluding the infiltration angle and forming an adhesion to the lens. United States Army Medical Museum negative 77205.

foci revealed that the alveoli were filled with endothelial leukocytes and a few polymorphonuclear leukocytes. The lesion was of proliferative character, and many of the endothelial leukocytes contained double-contoured yeast cells (fig 6).

The kidneys weighed 125 Gm each, and scattered throughout the cortex were multiple pinhead-sized, greenish nodules. On microscopic examination these were found to be multiple abscesses containing yeast buds.

The prostate gland was moderately enlarged, and scattered over the cut surfaces were multiple pinpoint areas of necrosis, from which there could be expressed a thick, greenish exudate. Microscopic study of sections from these areas revealed multiple abscesses (fig 7) with proliferation of cells, and in the

abscesses were many yeastlike cells, some of them surrounded by double-contour disks and others containing small buds (fig 8)

Exploration of the right patella revealed necrotic areas filled with greenish exudate, and in these areas yeast cells were also found on microscopic study. A few areas of osteoporosis were observed at the vertex of the skull, and the brain was entirely normal



Fig 10—Giant cell of the blastomycotic inflammatory reaction of the iris, showing budding and double-contoured yeast cells. United States Army Medical Museum negative 77205

Examination of the Eye—The eye was enucleated and submitted to the American Registry of Pathology of the Army Medical Museum for study. Report of the examination follows:

"The specimen consisted of a partially collapsed eye, measuring 24 by 24 by 24.5 mm. The pupil was small. The eye was opened between the horizontal

and the vertical plane. A dense, opaque lesion involved the ciliary body and the filtration angle on one side (fig 9). There were retinal folds around the optic disk. The vitreous was cloudy. The iris was bound down to the swollen lens.

"Clumps of polymorphonuclear leukocytes and large mononuclear wandering cells and lymphocytes clung to the posterior surface of the cornea. A small amount of serous exudate was present in the anterior chamber. There were exten-



Fig 11—Inflammatory process at the root of the iris, capsular cataract

sive posterior synechias and, on one side, an early anterior synechia. The iris was atrophic and diffusely infiltrated with plasma cells and lymphocytes, and an inflammatory pupillary membrane adhered to the anterior capsule of the lens. On one side a mass of inflammatory tissue involved the root of the iris and the ciliary processes and occluded the filtration angle and formed an adhesion to the lens. Tubercles were seen in the deep corneal lamellae and around the canal

of Schlemm. In the lesion were small abscesses, areas of necrosis, lymphocytes, plasma cells, epithelioid cells and giant cells. Throughout the mass and, in great numbers, in the giant cells (fig 10) were double-contoured bodies, among which budding forms were found. Beneath the inflammatory mass was a capsular cataract (fig 11). Lens fibers had undergone morgagnian degeneration. There was serous exudate beneath the detached ciliary body. Colloid excrescences were present on Bruch's membrane. There were degenerative changes in the retinal layer of rods and cones and small subretinal serous exudates. The lamina cribrosa was depressed.

"The diagnosis was blastomycotic iridocyclitis, cataract and secondary glaucoma."

Anatomic Diagnosis—The anatomic diagnosis was blastomycosis involving the skin, lungs, prostate gland, kidneys, bone and eye.

SUMMARY

A review of the literature and the study of a case of endogenous blastomycosis (Gilchrist's disease) are presented. Considering the widespread distribution of this disease throughout the body, it would not be unusual to find intraocular changes. From this case, and from other cases reported in the ophthalmic literature, one would conclude that metastatic uveitis associated with systemic blastomycosis is not so rare as has generally been thought. If the eye is implicated during the course of a fungous infection, I suggest the withdrawal of the plasmoid intraocular fluid for cytologic examination and culture. As a part of the postmortem examination, the histopathologic study of the ocular structures may prove helpful in demonstrating the protean manifestations of this disease.

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ACID BURNS OF THE EYE

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AND

H HERRMANN, M D

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THE more benign character of acid burns of the eye was first contrasted with that of alkali burns by George Joseph Beer in 1813, who stated that "the effect of mineral acids of equal saturation is rarely so destructive for the cornea as is slaked lime" Since then there have been numerous clinical reports of ocular injury by many types of acid¹ The patients whose cases have been reported received

From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital

1 (a) Rochat, G F Schädigung der Hornhaut durch Schwefelwasserstoff, *Klin Monatsbl f Augenl* **70** 152-154, 1923, abstracted, *Zentralbl f d ges Ophth* **10** 196, 1923 (b) Hensen, H Ueber einen Fall von Hornhauttransplantation nach Verätzung nebst Mitteilung über Beseitigung von Pseudopterygium der Hornhaut durch Thiersche Lappchen, *Klin Monatsbl f Augenh* **72** 172-175, 1924, abstracted, *Zentralbl f d ges Ophth* **13** 80, 1925 (c) Loree, M C Automobile Battery Burns of the Eyes and Adnexa with Case Reports, *J Michigan M Soc* **23** 292-294, 1924, abstracted, *Zentralbl f d ges Ophth* **14** 665, 1924-1925 (d) Stocker, F Praktische Bemerkungen zur Pathologie und Therapie der Schwefelwasserstoffkrankung der Augen *Med Klin* **1** 167-168, 1931, abstracted, *Zentralbl f d ges Ophth* **25** 298, 1931 (e) Becker Lippenschleimhaut-Frühplastik bei Limbusnekrose nach Schwefelsäureverätzung, *Klin Monatsbl f Augenh* **86** 384-385, 1931, abstracted, *Zentralbl f d ges Ophth* **25** 340 1931 (f) Oshima, T Zwei Fälle von Verätzung der Augen, des Gesichts, des Nackens und der Schultern durch Schwefelsäure, *Acta Soc ophth jap* **35** 295-296, 1931, abstracted, *Zentralbl f d ges Ophth* **25** 485, 1931 (g) d'Osvaldo, E Causticazioni da anidride acetica, abstracted, *ibid* **26** 656, 1932 (h) Kaminski, D Fall von beiderseitiger Verätzung der Augen mit Essigsäure, *Sovet vestnik oftal* **3** 378-380, 1933, abstracted, *Zentralbl f d ges Ophth* **31** 437, 1934 (i) Coppez, J H, and Brenta Brûlures oculaires par l'acide sulfurique, *Bull Soc belge d'opht* **72** 88-100, 1936, abstracted, *Zentralbl f d ges Ophth* **37** 432, 1937 (j) Berezinskaya, D Augenverätzungen mit Säuren und Alkalien, *Sovet vestnik oftal* **8** 319-332, 1936 abstracted, *Zentralbl f d ges Ophth* **37** 44, 1937 (k) Hisatomi, Y Ein seltener Fall von Augenverätzung durch Formalinlösung, *Chuo-Ganka-Iho* **31** 22-29, 1939, abstracted, *Zentralbl f d ges Ophth* **44** 671, 1939-1940 (l) Pollet-Delille, F Caracteres des brûlures accidentelles de l'oeil par l'acide chromique, *Bull Soc franç d'opht* **52** 221-225, 1939, abstracted, *Zentralbl f d ges Ophth* **45** 417, 1940

burns of varying degrees of severity. Those with mild burns recovered uneventfully regardless of the type of treatment whereas those exposed to high concentrations of acid usually had permanent corneal opacification perforation of the globe or extensive symblepharon. Since it is impossible to determine the exact degree of exposure from a history of the accident several investigators² have determined the tolerance of the rabbit eye for a few drops of various concentrations of different acids. These experiments have not yielded accurate quantitative data concerning the lowest p_H which the normal cornea will tolerate without injury, nor have they considered the penetrating power of the acid or the importance of the anion used.

In an introductory study of these problems Friedenwald, Hughes and Herrmann³ presented an outline of the methods used for the quantitative estimation of the acid-base tolerance of the rabbit cornea as follows. 1. Isotonic solutions which had a known p_H and, when possible, were well buffered were used. 2. Both the intact cornea and the cornea denuded of epithelium were irrigated for ten minutes with a standard amount of the test solutions, and 0.1 cc of the same solutions were injected intracorneally in other eyes. 3. A numerical estimation of the severity of several characteristic ocular symptoms produced by the acids was used to obtain a grade which could be manipulated statistically and graphically. With these technics results were obtained which were reproducible with a high degree of uniformity. It was found that the corneal epithelium had a highly protective effect against the penetration and damaging effects of acid. In addition, the corneal stroma itself was found to have some buffering capacity for solutions below p_H 4.0. However, ocular lesions were produced by exposure to isotonic solutions of hydrochloric acid of 0.005 normal concentration (p_H 2.5) or stronger or by exposure to isotonic solutions of citrate-phosphate-borate buffer at p_H 4.5 or below.

IMPORTANCE OF THE ANION

A plausible explanation of the discrepancy in the p_H levels at which lesions are produced by hydrochloric acid and the buffer solution is

(m) Winkler, A. Phenolverätzung beider Augen und Allgemeinflügel nebst einigen Bemerkungen über die Therapie von Augenverätzungen. *Klin. Monatsbl. f. Augenh.* **102**:810-815, 1939.

2. Siegrist, A. Konzentrierte Alkali und Säurewirkung auf das Auge. *Ztschr. f. Augenh.* **43**:176-194, 1920. abstracted, *Zentralbl. f. d. ges. Ophth.* **3**:220, 1920. Yoshimoto, R. Ueber experimentelle Säure- und Laugenverätzungen der Augen. *Arch. f. Augenh.* **99**:188-206, 1928. d'Osvaldo¹². Kaplan, J. D.: Erste Hilfe bei chemischen Verbrennungen der Augen. abstracted *Zentralbl. f. d. ges. Ophth.* **36**:391, 1936. Berezinskaya¹³.

3. Friedenwald, J. S., Hughes, W. F. Jr. and Herrmann, H. Acid-Base Tolerance of the Cornea, *Arch. Ophth.* **31**:279 (April) 1944.

to be found in the greater protein affinity of the trivalent anions of the buffer than of the chloride ion. Such an explanation would relate the tissue damage done by caustic acid solutions to the precipitation and denaturation of protein which these produce. In the present study we have put this hypothesis to direct test by comparing the effect on the cornea of various acid ions which are known to differ in their protein affinities. If the corneal damage depends on precipitation and denaturation of protein then the anions with greater protein affinity should produce lesions at higher p_H than the anions of lesser protein affinity, but the clinical and pathologic character of the lesions resulting from these various anions should be essentially the same. This is precisely the result shown by the experiments which we are now reporting.

The following acids, arranged in order of their increasing protein affinity and protein-precipitating ability, were used: hydrochloric, trichloroacetic, metaphosphoric, sulfosalicylic, picric, tungstic and tannic. Clinical reactions produced by solutions of these acids on the rabbit cornea were studied over a p_H range of 1 to 9. The solutions of the acids were brought to the desired p_H by addition of sodium hydroxide. In order to control the stability of the p_H and overcome the slight buffering capacity of the cornea itself, the acid solutions were buffered by addition of isotonic citrate-phosphate-borate solutions of the same p_H . Both buffered and unbuffered solutions were tested on rabbit cornea. The effect of the buffer solution alone was also tested.

The results of the experiments are shown in figure 1. The maximum lesions produced by these anions were similar in clinical appearance and in histologic characteristics. Except for their uniformity, these histologic and clinical observations have little bearing on the present argument and are therefore presented in subsequent sections. Corneal lesions were produced by chloride and trichloroacetate solutions (without added buffer) only up to p_H 3.0. The buffer solutions alone produced lesions up to p_H 4.5. Metaphosphate and sulfosalicylate solutions (with and without added buffer) produced lesions up to p_H 5.5 to 6.0. Picrate, tungstate and tannate solutions (with and without added buffer) produced lesions up to p_H 9.

The reaction produced by hydrochloric acid occurred at a somewhat higher p_H than was to have been expected by comparing its protein-precipitating power with that of the other agents used. However accurate data on the protein-denaturing effect of these solutions are not available, and our observations do not suffice to explain this small discrepancy.

Except for this irregularity with respect to hydrochloric acid, our experiments indicate that the anions with greater affinity for proteins produce corneal lesions at a higher p_H than the anions with lesser

protein affinity but that the maximum lesion produced by any one of these agents is essentially the same. Consequently, we may relate the clinical reactions to the formation of protein-anion combinations. Since the tissue damage is not reversed by return of the p_H to neutrality, it follows that the corneal proteins have been irreversibly changed, i. e., denatured by the process.

The possible role of penetrating power in relation to the severity of the lesions produced was tested by comparing the reaction to intra-corneal injection with that to irrigation after removal of the corneal epithelium, using the same solutions. It was found that all the anions tested except the chloride ion produced somewhat more severe reac-

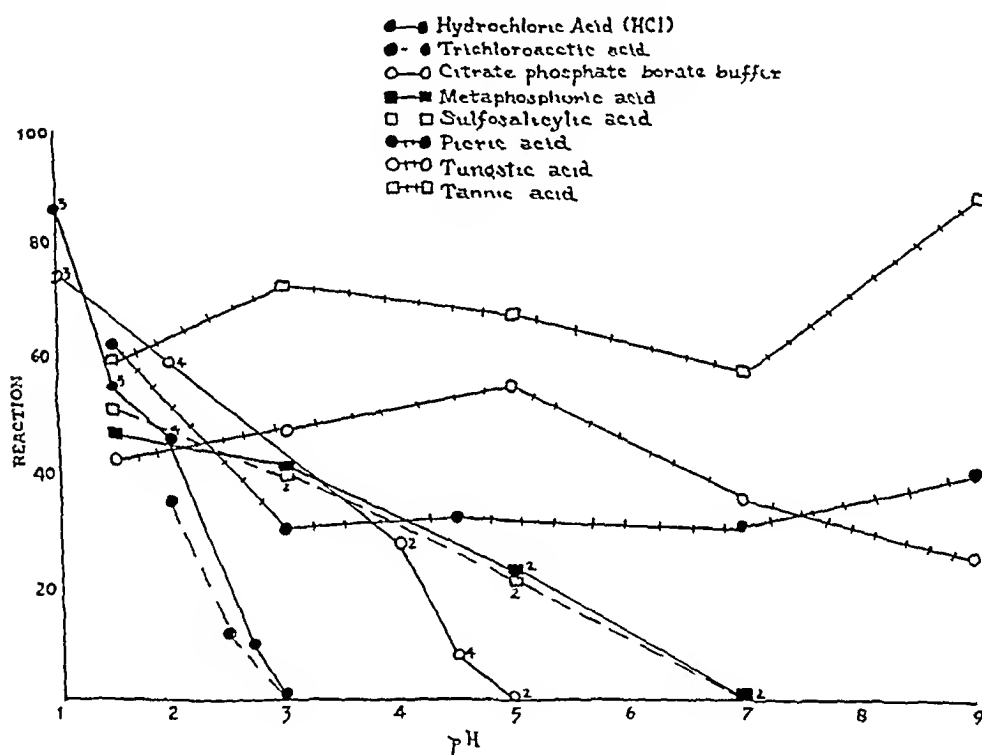


Fig 1—Severity of the reactions produced in the rabbit cornea by the intra-corneal injection of several acids of varying p_H , showing that anions with high protein affinity and protein-precipitating ability produce lesions at a higher p_H than anions with lesser protein affinity.

tions on injection than on irrigation. If the corneal epithelium was not removed, the severity of the corneal lesions after irrigation was, of course, much less.

CLINICAL CHARACTERISTICS OF ACID BURNS OF THE RABBIT CORNEA

Corneal opacification begins within a few seconds after the irrigation is started if the acid solution is concentrated (e. g., tenth-normal hydrochloric acid) or if the anion has a high protein affinity and protein-precipitating ability (e. g., trichloroacetic, sulfosalicylic or tannic acid). Severe corneal burns with various acids follow a similar clinical course.

- The sequence of events will therefore be described for a burn produced in a rabbit eye by irrigation for ten minutes with tenth-normal solution of hydrochloric acid made isotonic with sodium chloride

During Irrigation—A lacy network of fine punctate opacities appeared in the exposed area of the cornea, gradually coalescing into a smooth, dense opacification, through which the outlines of the pupil could hardly be seen. There was a sharp line of demarcation between the area immediately in contact with the irrigating fluid and that portion of the cornea which was loosely covered by the lids or the nictitating membrane. During the early stages of irrigation the corneal epithelium took a punctate green stain with fluorescein. However, later, the fluorescein produced only a yellow stain over the dense white opacity. The epithelium did not peel off in large sheets. The conjunctiva became moderately ischemic.

Twenty-Four Hours—There was a moderate amount of mucopurulent discharge, conjunctival redness and chemosis. Edematous thickening of the cornea could be made out with the hand slit lamp and loupe. The burned area remained sharply delimited from the clear cornea, which was protected during irrigation by the lids of the nictitating membrane.

Fourth Day—Much of the conjunctival reaction had subsided. There were ordinarily many dilated vessels at the limbus.

Seventh to Tenth Day—Many of the limbal blood vessels could be seen invading all layers of the cornea, either as large trunks and superficial loops or, less commonly, as straight brushlike projections into the deeper layers of the cornea. They most often proceeded around the edges of the area of densest opacification. Corneal edema was well developed by this time.

Fourteenth Day—Most of the eyes showed gross ulceration of the cornea, with perforation resulting in about one-half the severely burned eyes. This usually led to phthisis bulbi, although some perforations were repaired with an exuberant growth of fibrous and granulation tissue. If perforation did not occur, regression of the vascularization and corneal edema began, the corneal vessels becoming bloodless in two or three weeks. In less severely burned eyes the cornea might become clear except for a relatively thin but permanent, "silky" opacity. Symblepharon was not noted in any of the rabbits.

PATHOLOGIC CHARACTERISTICS OF ACID BURNS OF THE EYE

Rabbit eyes were irritated for ten minutes with a tenth-normal solution of hydrochloric acid made isotonic with sodium chloride, followed by brief irrigation with isotonic solution of sodium chloride. Specimens

were obtained immediately after the irrigation was stopped and forty-five minutes, two hours, eight hours, twenty-four hours, seven days and twenty-one days later. These were fixed in Zenker solution for twenty-four hours, washed for twenty-four hours and then dehydrated in alcohol. Hemotoxylin and eosin, Mallory's connective tissue stain and toluidine blue for metachromatic staining were employed (see figures).

Immediately After Irrigation—The cytoplasm of the corneal epithelium gave acidophilic staining reactions, and the superficial cells were desquamated.

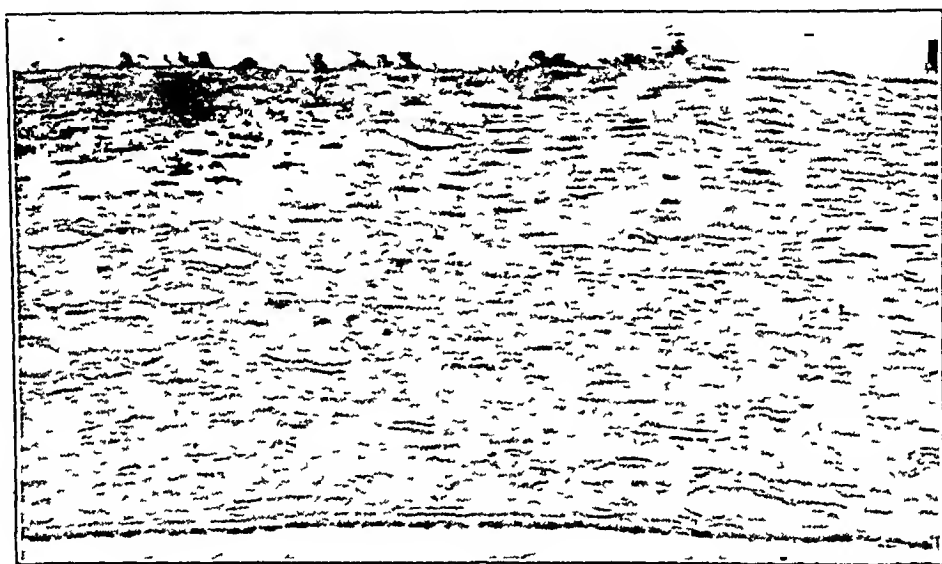


Fig 2—Section of cornea taken forty-five minutes after irrigation with tenth-normal hydrochloric acid for ten minutes. The sharp boundary of the lesion is well seen in the epithelium. The endothelium remains intact. $\times 100$

Forty-Five Minutes (fig 2)—Coagulated proteins appeared in the anterior chamber.

Two Hours—Albuminous material appeared under the corneal epithelium, and the corneal stroma was mildly edematous.

Four Hours—The corneal epithelium was greatly altered, and acidophilic granules appeared in the cytoplasm. There were some edema and fraying of the cells in the substantia propria, but the corneal endothelium appeared essentially normal.

Eight Hours—Sections (figs 3 and 4) demonstrated a sharp transition between the normal corneal epithelium and the burned epithelium, with acidophilic cytoplasm, pyknosis of the nuclei and general shrinking of the epithelial layer. With Mallory's connective tissue stain the epithelium was a deep maroon instead of a normal light red-

dish purple The stroma was edematous, and there were some obvious shrinking and disappearance of the cell nuclei

Twenty-Four Hours (fig 5) —Polymorphonuclear cells were found at the limbus entering the superficial layers of the stroma Metachromatic staining with toluidine blue showed no appreciable loss of mucoid

Seven Days (fig 6) —The corneal epithelium had regenerated over most of the burned area It was irregular, thin, degenerated and detached from the central portion of the stroma Blood vessels were found at the limbus in the anterior half of the corneal stroma The stroma itself

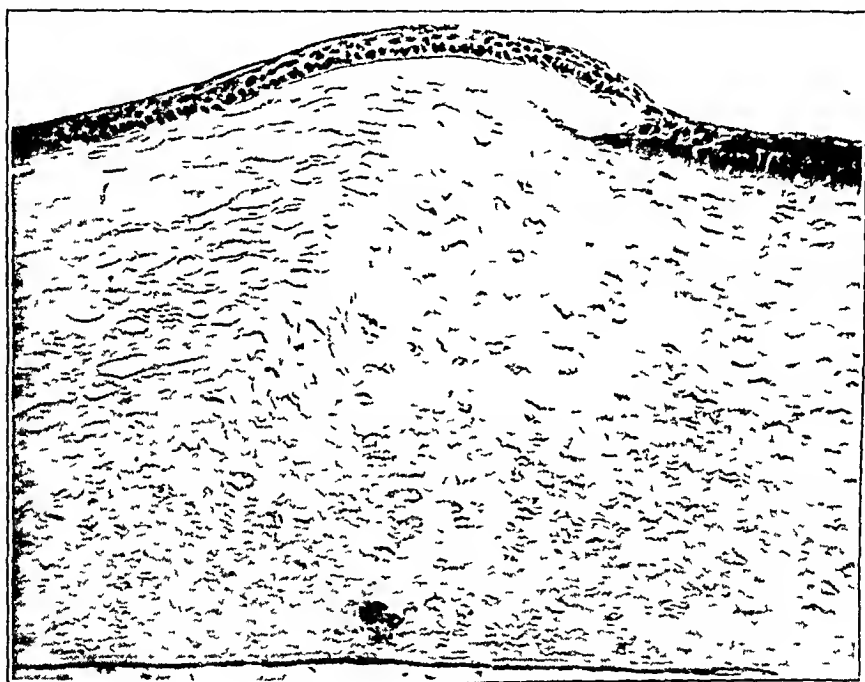


Fig 3—Section of cornea taken eight hours after irrigation with tenth-normal hydrochloric acid A slanting line of sharp contrast appears between the burned (left) and the normal (right) area Although the epithelium is thin and necrotic, there is no complete desquamation The texture of the stroma is altered, with loss of stromal cells $\times 100$

was edematous (fig 7) The endothelium had proliferated in places forming a layer several cells deep Metachromatic staining now showed almost complete loss of mucoid

Two to Three Weeks—An area of corneal ulceration was being repaired by proliferation of fibrous tissue and blood vessels, the crater of the ulcer being filled with inflammatory cells

In contrast to burns with alkalis and indelible dyes, the special characteristics of acid burns may be enumerated as follows (1) some-



Fig 4—Sections of cornea taken eight hours after irrigation with tenth-normal hydrochloric acid. *A* shows the pronounced pyknosis of nuclei in the basal layers of the involved epithelium. The cytoplasm is diminished and is more acidophilic. $\times 500$. *B* shows the contrast between normal stroma, on the right, and burned stroma, on the left. There are pronounced pyknosis and loss of nuclei in the involved area. Changes in the collagen fibers begin to be apparent. $\times 500$.

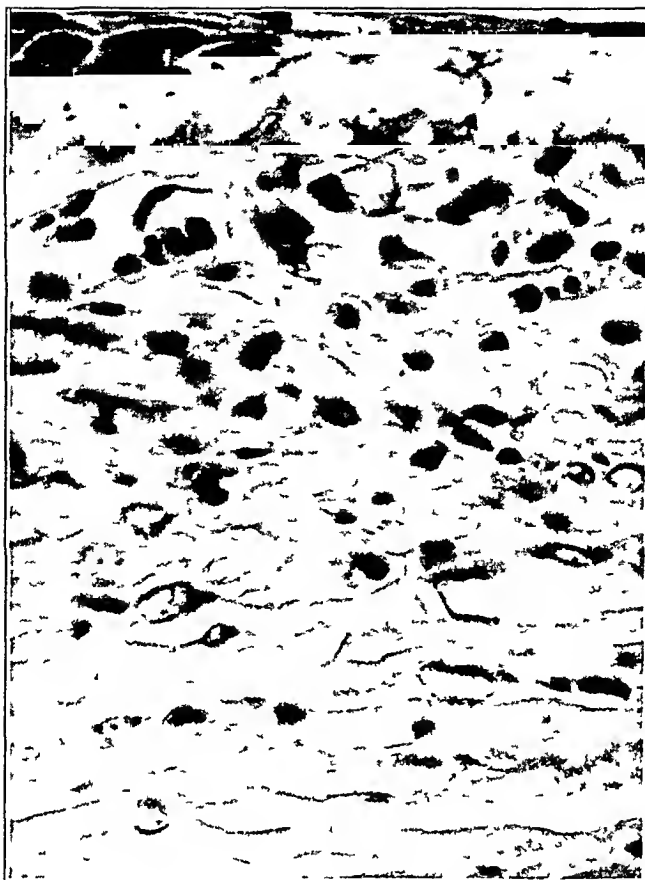


Fig 5—Section of cornea taken twenty-four hours after irrigation with tenth-normal hydrochloric acid, showing the infiltration of polymorphonuclear leukocytes in the anterior layers of the cornea near the limbus $\times 500$

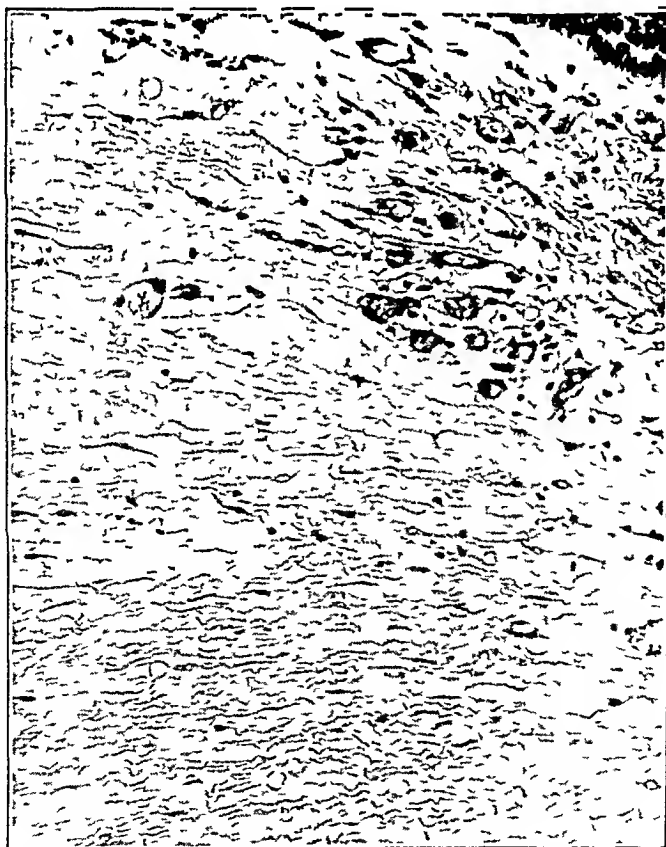


Fig 6—Section of cornea taken seven days after irrigation with tenth-normal hydrochloric acid, showing the vascularization in the anterior layers of the stroma extending in from the limbal vessels $\times 200$

what slower penetration into the eye, with rather sharp demarcation of the lesion, (2) a clinical course which can be prognosticated with some accuracy within a few hours after the injury (i.e., a lesion of nonprogressive type), (3) little tendency of the corneal epithelium to desquamate, (4) little tendency to exudative manifestations, such as purulent discharge with or without secondary infection, intense leukocytic infiltrations of the conjunctiva, cornea and iris, or fibrinous iritis, (5) little evidence of selective involvement of the blood vessels e.g. productions of intense early edema or petechial hemorrhages in the

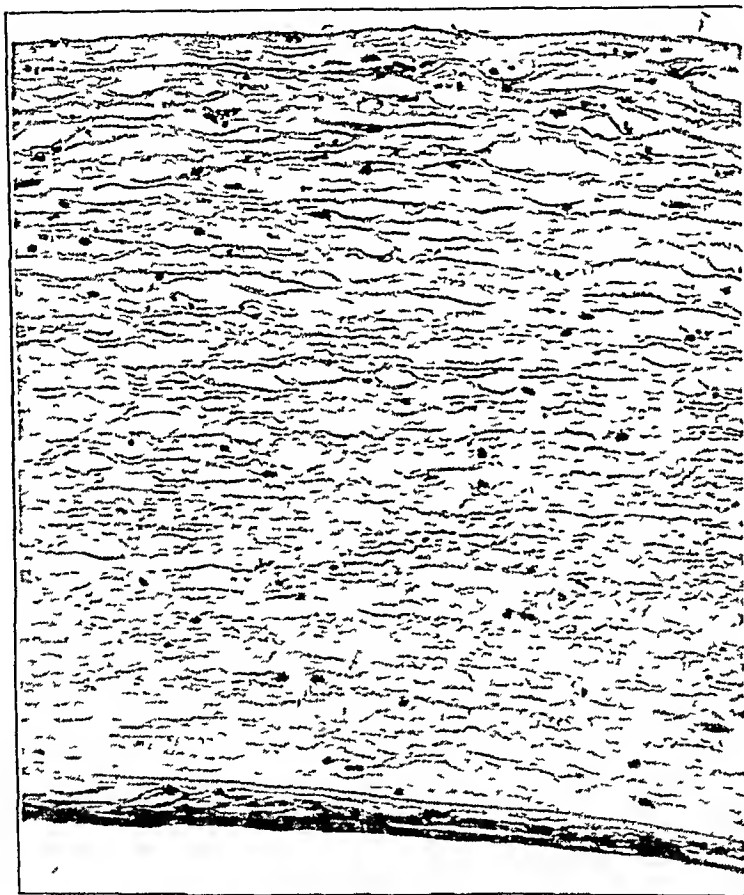


Fig 7—Section of cornea taken seven days after irrigation with tenth-normal hydrochloric acid, showing edema of the stroma, diffuse infiltration with polymorphonuclear leukocytes and reduplication of the endothelium. The epithelium is irregular and is not adherent to the stroma but is not completely desquamated. $\times 100$

conjunctiva or, later, of ischemia and thrombosis of the vessels around the limbus and in the iris, (6) marked tendency of the relatively opaque cornea to heal, and (7) no early loss of corneal mucoid (see next section)

EFFECT OF ACID ON CORNEAL MUCOID

Estimations of corneal mucoid were made by two methods (1) metachromatic staining with toluidine blue (1:1000) and (2) determina-

tions of the hexosamine content of the cornea, by Dr Karl Meyer and Dr Eleanor Chaffee⁴ In contrast to alkali-burned corneas, corneas exposed to irrigation with tenth-normal hydrochloric acid for ten minutes showed no early loss of metachromatic staining or hexosamine content However, after one week, metachromatic staining disappeared in the scarred areas, and the hexosamine content was reduced

CONCLUSIONS

Acid burns of the eye are essentially nonprogressive, and late relapses are uncommon The severity of the corneal lesion produced by acids is directly related to the protein affinity of the anion Anions with high protein affinity and protein-precipitating ability produce corneal lesions at a higher p_H than anions with low protein affinity, but these large anions (with high protein-precipitating ability) show poor penetration through the corneal epithelium and poor diffusibility in the stroma It is suggested that the clinical and pathologic characteristics of acid burns of the cornea may be explained by such precipitation and denaturation of the proteins of the cornea

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4 Drs Meyer and Chaffee, of Columbia University, determined the hexosamine content of acid-burned rabbit corneas and have permitted us to include the conclusions from their studies in the present report

TESTS FOR DETECTION AND ANALYSIS OF COLOR BLINDNESS

II Comparison of Editions of the Ishihara Test

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IN an earlier report on the Ishihara test for color blindness¹ we presented a brief history of the test from the original edition, issued in 1917, to the last Japanese edition of which we have a record in this country, the ninth edition, issued in 1940. Mention was also made of the British reprint of the ninth edition, issued in London in 1943.

That report is the first of a series designed to evaluate in turn various color tests as means of analyzing and detecting defective color vision. The data reported were collected during the course of a study of some 106 persons having defective color vision of varying types and amounts including 74 who had definite defects in color vision and 32 who had low, but normal, color vision. To study these persons a comprehensive battery of color tests was used, some of these are well known in the field of color blindness testing, some are less well known and some were devised in this laboratory. The fifth edition of the Ishihara test, one of the best known of the shorter editions, was selected for inclusion in the battery of tests. The results obtained from the entire battery aided in the classification of the defect in color vision as to type and extent and at the same time permitted us to evaluate each test of the battery both as a diagnostic or screening medium (the purpose of which is to screen out the subjects with defective color vision from those with normal color vision) and as a medium for classification (the purpose of which is to determine the type and extent of the defect).

Concerning the fifth edition of the Ishihara test, it was concluded that when properly administered the test affords a good rough device for screening persons with defective red-green vision from persons with normal color vision if a performance score of 60 is taken as the

From the Knapp Memorial Laboratories, Institute of Ophthalmology, Columbia University College of Physicians and Surgeons

1 Hardy, L H, Rand, G, and Rittler, M C. Tests for Detection and Analysis of Color Blindness. I. An Evaluation of the Ishihara Test, Arch Ophth 34 295 (Oct) 1945

critical score, that is, if 60 per cent of the plates are read correctly. In the group tested no subject with defective color vision scored more than 58 and no subject with normal color vision less than 75. The Ishihara test is, however, only a gross test for defective red-green vision. It fails to classify the type of defective color vision (protanopia, protanomaly, deuteranopia, deuteranomaly, tritanopia, tritanomaly²) and cannot be used to give a satisfactory evaluation of the extent of the defect, no matter how carefully administered.

Because the different editions of the test have undergone significant changes not only in the number of plates but in other important aspects, we undertook a comparative study of the responses given and the scores obtained on several representative editions by a small group of persons with defective color vision. Typical of the other changes in the later editions is a variation, whether intentional or not, in the hue, value and chroma (that is, in the color, brightness and saturation) of the disks forming both digit and background, and in some instances in the general brightness relation between digit and background, in the massing of color in digit and background and in the number of plates bearing a two digit pattern.

This comparative study was made with the fifth and seventh Japanese editions, the British reprint of the ninth Japanese edition, which we shall call simply the ninth edition, and the Ishihara plates included in the American Optical Company's compilation of pseudoisochromatic plates. Only the plates intended for testing color-blind literate subjects were used, of which there are 12 in the fifth edition, 24 in the seventh and ninth editions and 10 in the American Optical Company's test. These plates consist of six series. Series 1 and 2 are of the "transformation pattern" type, in which the subject with defective color vision sees a different pattern than the subjects with normal color vision sees, series 3 and 4 are of the "vanishing digit" type, in which the pattern is not seen at all by the subject with defective color vision, series 5 contains a "hidden digit," which is supposedly seen only by the subject with defective color vision, and series 6 is the "diagnostic" type, intended for classification as to deuteranopia and protanopia. A fuller description of the six series of plates is given in the former report¹. In the fifth edition there are 2 plates in each series, in the seventh and ninth editions, 4 plates in each series, and in the American Optical Company's test, 4 plates in series 1, 4 plates in series 2 and 2 plates in series 5.

2 For a simple explanation of these terms, see the preceding article in this series¹ (page 298, footnote 14), also, Hardy, L. H., and Rand, G. Recent Developments in Color Vision Testing, Graduate Lecture, Continuous Course no. 6 and 7, American Academy of Ophthalmology, 1944.

Twenty-two subjects with defective color vision to whom the entire battery of tests had been administered were available for the present work—7 deuteranomalous and 5 protanomalous subjects (anomalous trichromats) and 5 deuteranopes and 5 protanopes (dichromats). The testing distance was about 30 inches (76 cm). A close approximation to I C I Illuminant C was used throughout the work. The illumination on the test material was about 25 foot candles.

The general conclusion to be drawn from the study is that on the whole the three editions of the Ishihara test yield the same type of result, in spite of the changes that have been made in the number of plates and in the plates themselves, some of which are improved in one edition as compared with the others and others are less effective. The seventh and ninth editions have been improved over the fifth edition so far as trapping the protanomalous and protanopic types of subject is concerned, but the plates used for the classification of the type of red-green defective vision among the anomalous trichromats are less successful, particularly as reproduced in the seventh edition. None of the editions yields a differential score as to the extent of the defect in color vision. It seems probable from the data that the critical performance score of 60, marking the division between low normal and defective color vision, holds for the seventh and ninth editions of the test. This critical score, it will be remembered, was established for the fifth edition with the larger group of subjects, which included both observers with defective color vision and observers with low normal color vision. The Ishihara plates appearing in the American Optical Company's test are, however, for the most part poor selections and poor reproductions of the original Japanese plates and have less value for screening deuteranomalous and deuteranopic subjects than have the plates as reproduced by Ishihara.

The results are summarized in detail in tables 1 to 3. They will be discussed under three headings: (1) analysis of results obtained on the individual plates, (2) significance of performance scores on the entire test and (3) classification as to deuteranopia and protanopia and deuteranomaly and protanomaly.

ANALYSIS OF RESULTS OBTAINED ON INDIVIDUAL PLATES

In table 1 is shown for each type of defective color vision the percentage of subjects who pass the individual plates of each edition under consideration, the plates being designated by both series number and plate number as they appear in the edition under consideration. The first 4 horizontal rows of figures under each edition show these percentages for each type of defective color vision and demonstrate the value of the individual plates for detecting each type. The bottom

TABLE 1—Analysis of Results Obtained on Individual Plates of the Ishihara Test, Editions 5, 7 and 9 (British reprint), and the Ishihara Plates in American Optical Company's Test *

Type of Defective Color Vision	Number of Subjects	Percentage of Subjects with Each Type of Defective Color Vision Passing Individual Plates																							
		Series No 1			Series No 2			Series No 3			Series No 4			Series No 5			Series No 6								
		5th Edition (12 Plates) Plate No																							
Anomalous Trichromasy		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Deuteranomaly	7	57	72	0	0	0	14	14	29	14	0	0	0	0	0	0	0	43	29	14	0	41	57	43	43
Protanomaly	5	80	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	40	60	40	20
Dichromasy																									
Deuteranopia	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Protanopia	5	60	60	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	20	0	0	0	0	0
All types of defective color vision	22	30	39	0	0	0	0	5	9	9	5	9	9	9	5	9	9	14							
7th Edition (21 Plates) Plate No																									
Anomalous Trichromasy		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Deuteranomaly	7	43	14	0	14	0	0	0	0	14	14	0	0	29	29	0	0	43	29	14	0	41	57	43	43
Protanomaly	5	0	20	0	0	0	0	0	0	0	0	0	0	0	20	0	0	0	0	0	0	40	60	40	20
Dichromasy																									
Deuteranopia	5	0	0	20	0	0	0	0	0	0	0	0	0	0	20	0	0	20	0	0	0	0	0	0	0
Protanopia	5	0	20	0	0	0	0	0	0	0	0	0	0	0	20	0	0	0	20	20	0	0	0	0	0
All types of defective color vision	22	14	14	5	5	0	0	0	0	5	5	0	0	14	18	0	0	18	14	9	5	23	32	23	18
9th Edition, British Reprint, (24 Plates) Plate No																									
Anomalous Trichromasy		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Deuteranomaly	7	11	4	0	14	72	14	57	0	14	29	0	14	14	0	0	0	14	11	0	14	0	57	29	14
Protanomaly	5	20	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	60	20	
Dichromasy																									
Deuteranopia	5	0	0	0	0	20	0	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Protanopia	5	0	20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	20	0	0	0	0	
All types of defective color vision	22	18	23	0	5	27	0	23	0	5	9	0	5	5	0	0	0	9	9	5	14	5	6	11	9
Ishihara Plates, American Optical Company (10 Plates) Plate No																									
Anomalous Trichromasy		5	6	11	12	19	20	41	42																
Deuteranomaly	7	86	43	0	43	72	0	72	57																
Protanomaly	5	40	0	0	0	0	0	0	0																
Dichromasy																									
Deuteranopia	5	20	20	0	20	0	0	40	10																
Protanopia	5	40	0	0	0	0	0	0	0																
All types of defective color vision	22	50	18	0	18	23	0	32	27																

* Each plate is designated by a series number and a plate number as it appears in the edition under consideration

row shows the percentages for the subjects with defective color vision as a group

The following statements summarize the more obvious and significant changes found in the same plate as reproduced in the four editions and the effect of these changes on the percentage of subjects passing each plate

Series 1—The plates of this series are the most significantly changed in the later editions. They have been improved in the seventh and ninth editions but not in the American Optical Company's compilation. In the fifth edition the chief defect lies in the fact that the background disks (green) are too light and too uniform in value, or brightness. As was pointed out in the former report,¹ these plates fail to detect a majority of the subjects with the protanopic type of defective red-green vision because this type tends to see the "normal" digit, which is composed of dominantly reddish disks, as a dark pattern on a lighter background. In the seventh and ninth editions, more dark green disks are interspersed among the background disks, with the result that this criterion of brightness is no longer available to protanopes. These plates seem to be more critical for subjects of the deuteranomalous type also. In the American Optical Company's test, the background values used in the seventh edition are fairly well reproduced in the plates of series 1, but for some unknown reason the colored disks comprising the digit are lighter in value, lower in chroma and less blue in hue than in the seventh edition. The result is a much poorer plate for detection of the defect in color vision of subjects of the deuteranopic type, who tend to see the "normal" digit as a light pattern on a darker background. This plate illustrates the care that must be exercised when one is making polychromatic plates for testing defects in color vision to prevent any brightness clues from influencing the results.

Series 2—This series of plates as reproduced in the fifth and seventh editions is failed by all the subjects with defective color vision tested. As reproduced in the ninth edition and the American Optical Company's test, it is less selective in the case of deuteranomalous and deuteranopic subjects, apparently owing to a poor reproduction in both value and hue of the pigments used to form the digits.

Series 3 and 4—Our statistics show no significant difference in the results obtained with the plates of these series for the editions compared except that, as is usually the case, the two digit plates, which appear in the seventh and ninth editions, are more selective of defect in color vision than are the one digit plates, which appear in all the editions. These series are omitted from the American Optical Company's compilation, perhaps unfortunately, as they seem to be fairly good tests of defective red-green vision.

Series 5—In these plates, which contain a "hidden digit" supposedly seen only by subjects with defective color vision, the digit is composed of grayish blue and blue-red and blue-green disks of low chroma on a background of disks of high chroma, mostly yellow-red, yellow-green and dark yellow. In all but the fifth edition the digit stands out as a somewhat light, "ghostly" pattern, which is apparent to many if not most, persons having normal color vision. This series is passed by the smallest percentage of subjects with defective color vision as reproduced in the fifth edition. It is more selective of the deuteranopic type as it is reproduced in the seventh and ninth editions and of the protanopic type as it is reproduced in the American Optical Company's test. It is our belief that this series of plates is the least satisfactory in the Ishihara test, because a considerable number of persons having normal color vision see the hidden digit, thus failing the plate, while many who have an extreme defect in color vision fail to see it, thus passing the plate.

TABLE 2—*Significance of Performance Scores* for Subjects with Various Types of Defective Color Vision*

Type of Defective Color Vision	Number of Subjects	Average Score	Median Score	Range of Scores
5th Edition				
Anomalous Trichromasy				
Deuteranomaly	7	20	17	0-55
Protanomaly	5	16	17	5-55
Dichromasy				
Deuteranopia	5	0	0	0
Protanopia	5	13	17	8-17
All types of defective color vision	22	14	17	0-55
7th Edition				
Anomalous Trichromasy				
Deuteranomaly	7	16	17	0-35
Protanomaly	5	8	12	0-17
Dichromasy				
Deuteranopia	5	2	4	0-4
Protanopia	5	4	0	0-17
All types of defective color vision	22	9	6	0-33
9th Edition (British Reprint)				
Anomalous Trichromasy				
Deuteranomaly	7	19	21	0-42
Protanomaly	5	6	4	0-12
Dichromasy				
Deuteranopia	5	2	0	0-8
Protanopia	5	5	4	0-17
All types of defective color vision	22	9	4	0-42
Ishihara Plates, American Optical Company Test				
Anomalous Trichromasy				
Deuteranomaly	7	50	50	20-70
Protanomaly	5	8	0	0-30
Dichromasy				
Deuteranopia	5	18	10	0-50
Protanopia	5	4	0	0-10
All types of defective color vision	22	23	10	0-70

* Performance score is the percentage of the plates to which correct responses were given.

Series 6—The percentages of subjects passing this series of plates do not vary significantly for the different editions. The value of these plates for classification as to the type of defective red-green vision will be considered in connection with table 3.

SIGNIFICANCE OF PERFORMANCE SCORES ON ENTIRE TEST

Table 2 shows the performance scores obtained on the entire test for each of the editions of the Ishihara test under consideration and for the 10 Ishihara plates in the American Optical Company's test. In this table are given for each type of defect in color vision (*a*) the average score achieved by the group, (*b*) the median, or middle, score for each group, and (*c*) the range of scores, from lowest to highest, achieved by the individual subjects within each group. A score of 100 indicates that correct responses were given to all the plates of the test, a score of 0, that no correct responses were given, and scores between 0 and 100 indicate the percentage of plates to which correct responses were given. As in table 1, the first four rows of figures under each edition give the data for each type of defective color vision, and the bottom row gives the data for the subjects with defective color vision as a group.

The following points are brought out in table 2:

1. A comparison of the average and median performance scores and the range of performance scores for the different types of defective color vision does not reveal notable differences in the fifth, seventh and ninth editions of the Ishihara test, in spite of the many changes that have been made in the individual plates and in the number of plates. This is because in the later editions some of the plates have been improved but others have been made less effective. The most significant difference is in the lower scores achieved by the protanopic type of subject on the seventh and ninth editions as compared with those obtained on the fifth, owing to the improvement of the plates of series 1. Little, if anything, seems to have been gained by doubling the number of test plates in the later editions.

2. No cleancut separation as to extent or type of defect can be based on the performance scores achieved in any of the editions. While in general the dichromats had lower scores than the anomalous trichromats, a majority of the latter group had scores between 0 and 17, the range which included all the dichromats tested. Scores on the Ishihara test cannot, therefore, be used to indicate either the extent or the type of defect in color vision of the person being tested.

3. The 10 Ishihara plates as reproduced in the American Optical Company test are less effective for detecting deuteranomalous subjects and deuteranopes than are the fifth, seventh and ninth editions of the

test The scores for these subjects on the 10 plates are higher and the range of scores is significantly wider than on the original test This indicates either a poor selection of Ishihara plates for inclusion in the American Optical Company's test or a poor reproduction of the plates selected It is probable that both are contributive factors

In the former study¹ of 106 persons (74 subjects with defective and 32 subjects with low normal color vision) emphasis was laid on the fact that a critical performance score of 60 on the fifth edition of the Ishihara test was found to provide a cleancut separation between the scores of persons with normal color vision and those with defective color vision That is, no person with normal vision achieved a score below 75 and no person with defective color vision a score above 58 The number of subjects tested in the present study is too few to permit a similar determination of the critical score for the seventh and ninth editions of this test, also, no persons having low, but normal, color vision were included among those tested It may be pointed out, however, that the small group of subjects with defective color vision used in the present study is fairly representative of the larger group used in the earlier study This is seen in a comparison of the average and median scores and the range of scores obtained on the fifth edition by the larger group, which are given in table 2 of the former report,¹ with the scores obtained on the fifth edition by the smaller group, which are given in table 2 of the present report This comparison shows (a) that the median score for subjects with each type of defective color vision is exactly the same in the larger and in the smaller group, (b) that the differences in the average scores for subjects with each type of defective color vision in the two groups are insignificant and (c) that the range of scores is exactly the same for the deuteranomalous subjects and essentially the same for the other types of subjects with defective color vision in the two groups The range of scores is most different for the protanopes This is due to the presence of 1 person in the larger group of protanopes (17) who passed 4 plates (both the plates of series 1 and 5), scoring 33, and of 3 persons who did not pass any of the plates, scoring 0 The 5 protanopes of the smaller group passed either 1 or 2 plates, scoring 8 and 17, respectively Since no subject with defective color vision in the smaller group scored above 33 on the seventh edition or above 42 on the ninth edition and since there is no reason to expect persons with normal color vision to make lower scores on the seventh or the ninth edition than on the fifth edition, it seems permissible to conclude, at least until further data are available, that 60 can be taken as the critical performance score for the seventh and the ninth (British reprint) editions, as well as for the fifth edition of the Ishihara test That is, persons who on any of these editions score below 60 can be said as have defective color vision

As was stated in the previous report, the "Pseudo-Isochromatic Plates for Testing Color Perception," distributed by the American Optical Company, was included in the full battery of tests given our larger group of subjects, on the basis of which the classification as to type of defect in color vision was made. We have available, therefore, the results on the 10 Ishihara plates included in that test for 74 subjects with defective color vision and for 32 subjects with low normal color vision. Space will not be taken to present these results. An analysis of the data, however, shows that there is considerable overlapping of the scores attained not only among the subjects with the various types of defective color vision but between the subjects with defective color vision and the subjects with low normal color vision. For example, scores for the 23 deuteranomalous subjects ranged from 10 to 100, scores for the 12 protanomalous subjects, from 0 to 30, scores for the 15 deuteranopes, from 0 to 50, and scores for the 17 protanopes, from 0 to 10. The range of scores for the 74 persons with defective color vision is 0 to 100, and the range for the 32 subjects with low normal color vision, 60 to 100. It is obvious, then, that the American Optical Company's Ishihara plates, considered alone, do not furnish a critical score to differentiate persons with normal from persons with defective color vision, as is the case, according to our data, for the fifth edition of the Ishihara test and, in all probability, for the seventh and ninth (British reprint) editions.

CLASSIFICATION AS TO DEUTERANOPIA AND PROTANOPIA,
DEUTERANOMALY AND PROTANOMALY

So far we have discussed performance scores on different editions of the Ishihara test both as a means of detecting the presence of a defect in color vision and as a means of classifying the type of defect, and we have shown that the score achieved is adequate to separate subjects with defective color vision from subjects with normal color vision when the test is properly administered, but that it is not adequate to perform the equally important task of classifying the type and the extent of the defect. It remains to discuss the type of response to certain plates as reproduced in the different editions as a clue to this classification.

In the Ishihara test the plates of series 6 are the only ones designed for this purpose. There are 2 plates of this type in the fifth edition, 4 plates each in the seventh and the ninth edition and none in the American Optical Company's test. In these plates a double digit is presented (26, for example, on the first plate of series 6 in each edition). The left hand digit is composed of red disks, the right hand digit of red-purple disks and the background of gray disks. According to Ishihara, the subject with the deuteranopic type of defective red-green

vision will be able to read only the red digit, and the protanope, only the red-purple digit. Our data on the different editions have been analyzed to determine the effectiveness of these plates for this classification.

In scoring the responses to the plates, we used the criterion previously discussed¹. That is, a subject was called "classified" as to type of defect by the edition in question when one digit was read correctly and the other was not seen at all or was read incorrectly. When both digits were read correctly when neither was read correctly or when one was read incorrectly and the other not seen at all, the subject was called "not classified". In short, a "hit and miss" is necessary in order to utilize any plate of series 6 as a test for classification of the type of defect in red-green vision. It seems reasonable, also, to require a "hit and miss" on at least 50 per cent of the plates used for this purpose. The results obtained are shown in table 3.

TABLE 3—*Classification as to Deuteranopia and Protanopia, Deuteranomaly and Protanomaly*

Type of Defective Color Vision	Number of Subjects	Classification by at Least 50% of Plates		
		Correctly Classified, %	Incorrectly Classified, %	Not Classified, %
5th Edition				
Anomalous Trichromasy				
Deuteranomaly	7	86	0	14
Protanomaly	5	80	0	20
Dichromasy				
Deuteranopia	5	100	0	0
Protanopia	5	60	0	40
7th Edition				
Anomalous Trichromasy				
Deuteranomaly	7	57	0	43
Protanomaly	5	40	20	40
Dichromasy				
Deuteranopia	5	100	0	0
Protanopia	5	60	0	40
9th Edition (British Reprint)				
Anomalous Trichromasy				
Deuteranomaly	7	86	0	14
Protanomaly	5	60	0	40
Dichromasy				
Deuteranopia	5	100	0	0
Protanopia	5	60	0	40

The following points are brought out in table 3

1 The greatest number of subjects was correctly typed by the plates of series 6 as reproduced in the fifth edition, the next greatest number by the plates as reproduced in the ninth edition (British reprint) and the smallest number by the plates as reproduced in the seventh edition. These differences occur only in the number of anomalous trichromats successfully typed. All three editions give the same results for dichromats.

2 The plates are adequate to classify deuteranopes alone in all editions compared

CONCLUSIONS

The following conclusions concerning the editions of the Ishihara test studied seem justified

1 A comparison of the average scores and the range of scores for the different types of deficiency in color vision does not reveal notable differences in the fifth, seventh and ninth (British reprint) editions of the Ishihara test, in spite of the changes made in the number of plates and in the plates themselves, some of which are improved and some of which are made less effective. The most significant difference is in the results for the observers of the protanopic type which are due to the improvement of the plates of series 1 in the seventh and ninth editions

2 Properly administered, the three editions of the Ishihara test afford a good rough device for screening persons with defective from persons with normal color vision if a performance score of 60 is taken as the critical score. In the groups tested in this study and in the former study of the fifth edition of the test,¹ no person with defective color vision scored more than 58 and none with low normal color vision less than 75. A critical score cannot, however, be established for the 10 Ishihara plates reproduced in the American Optical Company's test. Tested with this group of plates, some subjects with defective color vision passed all the plates, scoring 100, and some with low normal color vision passed only 6 of the plates, scoring 60

3 No analysis as to type or extent of defect in color vision can be based on performance scores

4 The plates of series 6 as reproduced in the fifth edition are the best for correctly classifying the type of anomalous trichromasy, those of the ninth edition the next best and those of the seventh edition the poorest. All three editions give the same classification of the type of dichromasy

5 Nothing seems to be gained by doubling the number of plates, as is done in the seventh and ninth editions

6 Other things being equal, plates bearing two digits afford better tests of defective color vision than plates having only one digit

In brief, the general conclusions drawn from a study of a larger number of subjects for the fifth edition of the Ishihara test hold also for the seventh and ninth (British reprint) editions but not for the Ishihara plates as reproduced in the American Optical Company's test

EDEMA OF CORNEA PRECIPITATED BY QUINACRINE (ATABRINE)

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GENERAL CONSIDERATIONS

THE avascularity and transparency of the cornea permit study of early pathologic alterations to a degree not possible in other tissues. The slightest edema or most minute infiltration causes immediate changes in transparency. Alteration in the colloidal properties and the water content of the "corneal gel" leads to increased dispersion and refraction of light and augmentation of the normal Tyndall phenomenon, e g, increases in relucency. It must be remembered that what is observed grossly or with the slit lamp and corneal microscope is the alteration in optical phenomena which result from changes in the tissues.

According to Fischer,¹ the normally clear cornea contains 76 per cent of water, and an additional 10 per cent may lead to clouding. When the fluid is gathered in droplets the light is irregularly dispersed, producing a relucient haze. As it affects the epithelium, this is commonly called "bedewing." This physical process of imbibition is completely reversible.

Edema forms the most common clinical pathologic manifestation of the corneal epithelium and occurs in nearly all corneal disturbances, both inflammatory and degenerative. It may be seen in conjunction with edema of deeper layers of the cornea. Duke-Elder² listed the common causes of corneal edema as including trauma, inflammation, degeneration and increased intraocular tension. Injury may be anatomic or physiologic, irrigation with distilled water or instillation of cocaine will produce edema of the epithelium. In glaucoma the elevated intraocular pressure is thought to force an increased amount of aqueous into the corneal tissue through the trabeculae at the angle of the anterior chamber.

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1 Fischer, cited by Duke-Elder,² p 1845

2 Duke-Elder, W S. Textbook of Ophthalmology, London, Henry Kimpton, 1939, vol 2, p 1846

Berliner³ mentioned interference with the antidromic impulses of the corneal nerves as a basis for epithelial edema, presumably through the accumulation of cellular metabolites. He also included allergy as a possible factor in such corneal changes. Finally, Duke-Elder stated that constitutional causes may be responsible for corneal edema. He cited reports by Aubineau⁴ and, later, Marbaix⁴ describing cases of this type in patients with elevated blood cholesterol. The lipid imbalance was thought to be the causative factor, and the corneal edema subsided with appropriate dietary treatment.

CLINICAL ASPECTS

During the past eighteen months a number of patients have been seen in the southwest Pacific area with bilateral haziness of the cornea of obscure origin. During the eight months from August 1944 through March 1945, inclusive, 4 such patients were studied in some detail at the hospital at which we are stationed. Examination with the slit lamp and the biomicroscope disclosed innumerable fine granular opacities evenly dispersed over the area of the cornea. These were apparently located primarily in the epithelium and, to a lesser extent, in the underlying superficial layers of the corneal parenchyma. The clinical picture was that of bilateral superficial corneal edema, and, as might be expected, the process was completely reversible. There were no associated signs of ocular inflammation, and there were no changes suggestive of glaucoma. Each of these patients was receiving the required protective dose of quinacrine (atabrine).

REPORT OF CASES

CASE 1—An infantry private aged 20 noticed gradually increasing blurring of vision, beginning about July 27, 1944, while on jungle patrol in Aitape, New Guinea. He had no associated systemic complaints and no ocular irritation, pain, redness or conjunctival discharge. The impairment of vision was present at all distances and was experienced particularly at night, when there was a pronounced dispersal of lights. He noted no floating spots before the eyes and no defects of the visual fields. There was no history of a previous similar episode. The patient had never worn glasses, and vision had been excellent.

He had been in the tropics only one month prior to onset of this complaint. There was no history of injury to the eyes or of undue exposure to brilliant sunlight, dust or irritants. For four weeks his diet had consisted of C rations, with no fresh foods.

The only medicament received by the patient was quinacrine hydrochloride, and he had been taking 1 tablet (0.1 Gm) daily for about six weeks.

On August 9 he was admitted to an evacuation hospital and was transferred to a station hospital at this base. Vision was recorded as 20/50 — 2 in the right

3 Berliner, M. L. *Biomicroscopy of the Eye*, New York, Paul B. Hoeber, Inc., 1943, vol. 1, p. 393.

4 Cited by Duke-Elder,² p. 1848.

eye and 20/40 — 3 in the left eye. There was described a diffuse haziness of the substantia propria as the only positive finding. Treatment included administration of multivitamins, instillation of atropine and application of hot compresses. Vision gradually improved to 20/20 — in each eye, and the patient was discharged to duty. However, at this time there was still some blurring of vision, which was most conspicuous at night.

About September 25 he again noticed gradually increasing visual impairment of the type previously experienced. He was again hospitalized on October 9 and was returned to the station hospital. Vision on this second admission was recorded as 20/40 — 2 in the right eye and 20/40 in the left eye.

Consultation at this general hospital then disclosed a diffuse haziness of the corneas due to finely dispersed punctate opacities, which seemed to be most numerous in the superficial corneal layers. The epithelial surface, however, was smooth, and at that time there was no staining with fluorescein. There was no evidence of intraocular inflammation, in each eye the anterior chamber, iris, lens, vitreous and fundus were normal.

There was no tenderness on palpation, and the intraocular tension was normal as read at various hours of the day.

Determination of the visual fields disclosed normal peripheral limits. The blindspot measured 6 by 8 degrees in the right eye and 6 by 8 degrees in the left eye (1 mm white test object at 33 cm). There was no significant error of refraction.

A complete medical investigation revealed no evidence of systemic disease. Consultations with members of the dental, otolaryngologic and urologic staffs revealed no foci of infection. Blood counts and urinalysis gave normal results, the Kahn reaction was negative, and a smear revealed no malarial organisms. Cutaneous reactions were negative to tuberculin (purified protein derivative) in both dilutions. A patch test for quinacrine was negative. Treatment at the station hospital again consisted in the use of atropine, hot compresses and multivitamins. After two months' observation vision had improved only to 20/30 in each eye.

On Jan 4, 1945 the patient was transferred to this general hospital, with visual acuity of 20/30 in the right eye and 20/30 in the left eye. Examination with the slit lamp still showed diffuse haziness of each cornea due to a fine stippling of punctate opacities, located largely in the most superficial layers. Again there was no staining with fluorescein, and the eyes were otherwise normal.

No causative factor for this corneal edema had been found after extensive investigation and observation. The patch test for quinacrine had been negative, and the patient had continued to receive the usual 0.1 Gm daily dose of the drug. In an attempt to rule out idiosyncrasy to quinacrine it was decided (1) to stop the drug for one month and (2) to administer larger doses of quinacrine.

The patient was given no quinacrine from January 4 through February 3. During this interval vision improved to 20/20 in the right eye and 20/20 in the left eye, but there were still a few residual opacities, and vision continued to be somewhat blurred, with dispersal of lights at night.

On February 4 an intensive course of quinacrine therapy, comparable to that used in treatment of malaria, was started. This regimen consisted in administration of divided doses of the drug, totaling 12 Gm the first day, 0.8 Gm the second day and 0.4 Gm on each of the succeeding four days. He was then continued on a regimen of 0.2 Gm daily through February 16.

For eight days after the beginning of quinacrine therapy there was no appreciable change in the corneal condition. On February 12 the patient noticed

increasing blurring of vision, but again without any redness or irritation of the eyes. On February 16 vision had decreased to 20/100 in the right eye and 20/100 in the left eye. Examination showed no conjunctival injection, but the cornea was diffusely hazy, giving an appearance of ground glass. The opacities were of the type previously described but much more dense, and on this occasion there were many fine punctate erosions of epithelium, which stained with fluorescein. After quinacrine therapy was discontinued, on February 16, the cornea gradually cleared, e g, vision was 20/40 in each eye on February 23. By March 17 it was 20/20 in each eye, and there was only slight dispersal of lights at night. After two months without quinacrine vision was 20/20 in each eye, and the patient noted only the slightest dispersal of lights. The cornea was then normal on all examinations.

While receiving the intensive course of quinacrine treatment, the patient experienced some nausea, anorexia and slight abdominal distress, but he did not vomit. He had moderate malaise and lost 5 pounds (2.3 Kg) in weight. Examination showed no abdominal distention and no enlargement or tenderness of the liver. The scleras were not discolored. However, there were a moderately elevated icteric index, of 15, and impairment of hepatic function as revealed by the hippuric acid excretion test, e g, an excretion of 1.6 Gm of hippuric acid and 1.1 Gm of benzoic acid, per hundred cubic centimeters. The medical consultant made a diagnosis of "hepatitis with subclinical icterus." The sedimentation rate remained normal, as did the serum protein content. After discontinuation of the drug, on February 16, the anorexia and vague abdominal distress gradually subsided, and the patient had more than regained the lost weight at the end of four weeks. On March 27 the hippuric acid excretion test showed improvement, e g, an excretion of 3.2 Gm in terms of hippuric acid and of 2.2 Gm in terms of benzoic acid, per hundred cubic centimeters, and the general physical condition was again entirely normal.

CASE 2—A 20 year old private in the Quartermaster Corps noticed gradually increasing blurring of vision, beginning about Aug 1, 1944, while en route from Oro Bay to Finschhafen, New Guinea. There were no associated systemic complaints and no ocular irritation, pain, redness or conjunctival discharge. The visual impairment was present at all distances and was particularly troublesome at night, when there was pronounced dispersal of lights. He observed no floating spots before the eyes and no defects in the visual fields. There was no history of a previous similar episode.

The patient had been in the tropics only one month prior to the onset of this complaint. There was no history of injury to the eyes or of undue exposure to brilliant sunlight, dust or irritants. For seven weeks prior to the onset of visual disturbance his diet had consisted of C rations, with no fresh meats, fruits or vegetables. The only medicament which he had received was quinacrine hydrochloride, and he had been taking 1 tablet (0.1 Gm) of this drug daily for approximately six weeks.

On admission to this general hospital, on August 3, vision was 20/70 in the right eye and 20/100 in the left eye, with correction it was 20/50 in the right eye and 20/70 in the left eye. Examination showed diffuse haziness of each cornea, due to a fine stippling of punctate superficial opacities. Examination with the slit lamp and corneal microscope indicated that these were located primarily in the basal layers of the corneal epithelium. The epithelial surface, however, was smooth, and at that time there was no staining with fluorescein. There was no conjunctival or circumcorneal injection and no evidence of intraocular inflammation, the ocular media were apparently clear and the fundi normal.

There was no tenderness on palpation, and the intraocular tension was normal on repeated readings at various hours. The visual fields showed normal peripheral limits, and the blindspots were of average size, measuring 5 by 7 degrees in the right eye and 5 by 7 degrees in the left eye (1 mm white test object at 33 cm). Refraction indicated a moderate degree of compound myopic astigmatism, as follows: right eye —1.00 D sph —0.75 D cyl, axis 90, left eye —1.00 D sph —0.75 D cyl, axis 90.

Complete medical investigation on his admission disclosed no evidence of systemic disease. Dental, otolaryngologic and urologic consultants reported no foci of infection. Blood counts and urinalyses showed nothing abnormal, the Kahn reaction of the blood was negative, and a smear revealed no malarial organisms. Cutaneous reactions were negative to tuberculin (purified protein derivative) in both dilutions. A patch test with powdered quinacrine gave a negative reaction.

The patient was not given any ocular treatment for three weeks, and with correction vision gradually improved to 20/30 in each eye. There was some fluctuation in the density of the opacities and the visual acuity from day to day. Quinacrine was then discontinued for four weeks, and vision improved to 20/20 in each eye, but there was still slight blurring, with dispersal of lights at night. Quinacrine therapy was resumed, with 1 tablet (0.1 Gm) daily for two weeks, without apparent alteration in the residual corneal edema, and on October 3 the patient was discharged to duty. About one month later he noticed a gradual increase in blurring of the type previously experienced. During the succeeding eight weeks the visual impairment became so pronounced as to interfere seriously with the performance of duty, and he was readmitted to this general hospital on December 29. Vision with correction was then 20/40 in each eye, and examination showed fine superficial corneal opacities, identical with those described on the original admission. The patient was given polyvitamins, 2 tablets, and riboflavin, 2 mg, three times daily.

No causative factor for this corneal edema had been found after extensive investigation and observation. The patch test had been negative for quinacrine, and the patient had continued to take the usual 0.1 Gm daily dose of the drug. In an attempt to rule out idiosyncrasy to quinacrine, it was decided (1) to stop the drug for one month and (2) to administer larger doses of quinacrine.

No quinacrine was received from Jan 4, to Feb 4, 1945. During this period vision with glasses again improved, being 20/20 — in each eye. However, there still remained the occasional residual opacities, with subjective blurring and dispersal of lights at night.

On February 4 an intensive course of quinacrine therapy, comparable to that used in the treatment of malaria, was started. This regimen consisted in divided doses of the drug, totaling 12 Gm the first day, 0.8 Gm the second day and 0.4 Gm on each of the succeeding four days. The patient had some nausea and vomiting, particularly on the first two days of treatment, but he was able to retain the full six day dose of quinacrine, the dose was then reduced to 0.2 Gm daily through February 16.

For six days after beginning quinacrine therapy there was no change in the corneal condition, but on February 10 he noticed increasing blurring of vision, with slight irritation, redness and tearing. By February 16 vision with correction had decreased to 20/70 in the right eye and 20/50 — 1 in the left eye. Examination showed moderate injection of the conjunctiva with diffuse superficial haziness of the cornea. However, there were now many punctate erosions of the epithelial surface, which stained with fluorescein and were not present with previous episodes of corneal edema. After discontinuation of quinacrine on February 16, corneal

edema gradually subsided, and vision had improved again to 20/20 in each eye by February 26. However, the residual punctate opacities and a few erosions of the epithelium were slow in clearing, and after eight weeks an occasional punctate erosion could still be detected with the slit lamp. The cornea was now clearer than at any time during the past eight months, and the patient stated that the dispersal of lights at night had almost completely disappeared.

On February 4 and 5, at the beginning of the course of quinacrine treatment, the patient was nauseated and vomited several times. He complained of increasing anorexia, malaise and tenderness in the right upper quadrant of the abdomen but had no further vomiting. He had lost at least 10 pounds (4.5 Kg) in weight by February 23, when examination disclosed moderate abdominal distention and ascites, with a fluid wave. The liver was enlarged and tender, extending 2 fingerbreadths below the costal margin. The scleras were never icteric. Laboratory tests reported an elevated corrected sedimentation rate of 26 mm in one hour and reduced excretion of hippuric acid—19 Gm in terms of hippuric acid and 13 Gm in terms of benzoic acid, per hundred cubic centimeters, the icteric index was 12. A diagnosis of "hepatitis with subclinical icterus" was made by the medical consultant. With rest in bed, the patient showed steady clinical improvement over a two week period. The anorexia, malaise and abdominal discomfort disappeared. By March 10 the liver was no longer enlarged or tender and there was no ascites. However, the increased sedimentation rate and the diminished excretion of hippuric acid persisted without change for two months, although the patient had no abdominal complaints and clinically seemed to be fairly normal.

CASE 3—A 29 year old infantryman noticed sudden onset of blurring of vision in each eye on Aug 21, 1944, at Aitape, New Guinea. During the previous night he had complained of transient bifrontal headache but had no other symptoms suggestive of systemic disease. There was no associated ocular irritation or pain and no redness, tearing or conjunctival discharge. The impairment of vision was present at all distances and was most troublesome at night, when there was a pronounced dispersal of lights. He observed no floating spots before the eyes and no defects of the visual fields.

The patient had served nineteen months in tropical New Caledonia and the Solomon Islands and five weeks in New Guinea, after a three month interval in New Zealand. His general health had been excellent. There was no history of injury to the eyes or of undue exposure to brilliant sunlight, dust or irritants. The diet had consisted largely of C rations, with only occasional fresh meat or eggs.

Quinacrine hydrochloride was the only medicament received. He had been taking this drug for twenty-one months, as follows: November 1942 to July 1943, $\frac{1}{2}$ tablet (0.05 Gm) daily; July 1943 to July 1944, 1 tablet (0.1 Gm) daily, and during the latter part of July and the month of August 1944, 2 tablets (0.2 Gm) daily. The last period was from the date of landing in New Guinea until his admission to the station hospital, on Aug 30, 1944. The dose of quinacrine hydrochloride was then reduced to 0.1 Gm daily during hospitalization.

At the station hospital, on September 1, vision was recorded as 20/70 in each eye. There were described fine granular superficial opacities of each cornea, giving a steamy appearance. The patient was evacuated to this general hospital with a diagnosis of "corneal edema."

On his admission, on September 4, vision had improved to 20/40 in each eye. Examination revealed diffuse haziness of each cornea due to innumerable fine punctate opacities. Examination with the slit lamp and biomicroscope showed

these to be located in the superficial layers of the cornea, and primarily in the epithelium. At that time, however, the epithelial surface was smooth and did not stain with fluorescein. There was no evidence of intraocular inflammation, the ocular media were apparently clear and the fundi normal. There was no tenderness on palpation. Intraocular tension was normal on repeated examinations at various hours. Examination of the visual fields indicated normal peripheral limits, the blindspot measured 7 by 5 degrees in the right eye and 7 by 5.5 degrees in the left eye (1 mm white test object at 33 cm).

Complete medical investigation on his admission disclosed no evidence of systemic disease. Consultations revealed no foci of infection in the sinuses, the teeth or the prostate gland.

Laboratory tests on admission, including blood counts, determination of the sedimentation rate and urinalysis, gave normal results. The Kahn reaction of the blood was negative, and a smear revealed no malarial organisms. Cutaneous reactions were negative to tuberculin (purified protein derivative). A patch test for quinaerine gave a negative reaction.

The patient was given no treatment during the first week in this hospital, and vision had improved to 20/20 in each eye by Sept 11, 1944. It was at first thought that he could be discharged to duty, but the subjective blurring persisted, with fluctuations, vision varying from 20/20 to 20/30 in each eye. He was given 2 capsules of polyvitamins and 2 mg of riboflavin three times daily over a ten week period, without clearing of the residual corneal edema.

In late November 1944 he began to experience sporadic anorexia, vague epigastric discomfort and "heart burn". Repeated examinations of the abdomen revealed nothing abnormal. Because of persisting symptoms, a series of roentgenographic studies of the gastrointestinal tract were made on Jan 5, 1945, but no abnormality of the stomach or the duodenum was disclosed.

No causative factor for this corneal edema had been found after extensive investigation and observation. The patch test for quinaerine had been negative, and the patient had continued to receive the usual 0.1 Gm daily dose of the drug. In an attempt to rule out idiosyncrasy to quinaerine, it was decided (1) to stop the drug for one month and (2) to administer larger doses of quinaerine.

No quinaerine was administered from Jan 4 through Feb 3, 1945. There seemed to be further subjective clearing of vision, which was again recorded as 20/20 in each eye. Only occasional punctate opacities remained at the end of this period. The vague abdominal complaints likewise largely subsided.

An intensive course of quinaerine therapy, comparable to that used in treatment of malaria, was then started. This regimen consisted in administration of 1.2 Gm the first day, 0.8 Gm the second day and 0.4 Gm on each of the succeeding four days. However, he began to vomit on the second day of treatment, and on the fourth day administration of the drug was discontinued because of inability to retain the medicament. There was aggravation of abdominal complaints.

There was no change in the corneal condition for eleven days after administration of the drug was started, but on February 15, seven days after quinaerine had to be discontinued, there began to develop blurring vision, due to increasing numbers of the fine punctate opacities. On February 18 visual acuity was 20/40 in each eye, and on February 22 it had dropped to 20/50 in the right eye and 20/70 in the left eye. Again the slit lamp showed innumerable fine superficial corneal opacities involving the epithelium and the superficial layers of the stroma. For the first time, however, there were many superficial punctate erosions of the epithelium, which stained with fluorescein. Thereafter vision steadily improved, as the density of the opacities decreased. On February 25 vision was 20/40 in

each eye, on February 27, 20/30, and on March 5, 20/20. On April 1 vision was a full 20/20 in each eye and no corneal opacities could be detected with the ophthalmoscope or the slit lamp.

During this same period the patient's abdominal complaints became accentuated, with pronounced cramping, nausea, vomiting and distention. On February 19 the liver was enlarged and tender and there was definite ascites. Clinical icterus was present, and numerous spider nevi were evident over the face and trunk. Laboratory tests revealed icteric indexes averaging 40 and total plasma proteins of 6.1 Gm with 2.6 Gm of albumin and 3.5 Gm of globulin, per hundred cubic centimeters. The ascites rapidly increased, and diuresis was not obtained with intravenous injection of 50 per cent dextrose, serum albumin and mercurophylline. Abdominal paracenteses were performed on March 13 and again on March 23, 1945, 4,000 cc of clear fluid being obtained on each occasion. The patient ran a moderate fever, with elevation of temperature as high as 101 F, this was not appreciably affected by treatment with penicillin. He was given a preparation of vitamin K in large doses to combat persistent and recurrent bleeding from the gums and from a spider nevus on the right cheek.

Finally, on March 30, diuresis was induced, and the ascites gradually subsided without further treatment. The icteric index was 35 on April 4, and the total plasma proteins measured 6.6 Gm, with 3.5 Gm of albumin and 3.3 Gm of globulin, per hundred cubic centimeters. By May 1 the ascites had completely disappeared, and the icteric index had dropped to 12. The patient's general condition was much improved, and his convalescence from the severe hepatitis was progressing satisfactorily.

CASE 4—A 29 year old corporal, a wireless operator, had rapidly increasing blurring of vision in each eye, which began on Oct 17, 1944. He had no associated systemic complaints and no ocular irritation, pain or redness or conjunctival discharge. The impairment of vision was present at all distances and was particularly pronounced at night, when there was marked dispersal of lights. There were no floating spots before the eyes, and no defects of the visual fields were noted.

Prior to onset of this complaint the patient had served eight months in New Guinea. In March 1944, one month after arriving in the tropics, he experienced a similar attack of blurred vision, for which he was treated at a field hospital. His vision gradually improved without specific treatment, and he was discharged to duty in six weeks. However, there was residual blurring of such degree that he was unable to resume his previous duties as wireless operator.

There was no history of injury to the eyes or of undue exposure to brilliant sunlight, dust or irritants. His diet had consisted of the usual C rations, with no fresh foods.

The only medicament received by the patient was quinacrine hydrochloride, and he had been taking 1 tablet (0.1 Gm) of the drug daily during the eight months of tropical service.

On Oct 19, 1944 he was admitted to a station hospital, visual acuity was recorded as 20/50 in each eye and was not improved with lenses. Examination disclosed a diffuse granular haziness of each cornea. Study with the slit lamp and corneal microscope in consultation at this general hospital showed that these finely dispersed punctate opacities were located in the superficial corneal layers, but the epithelial surface was smooth and did not stain with fluorescein. There was no evidence of intraocular inflammation, in each eye the anterior chamber, iris, lens, vitreous and fundus were of normal appearance.

There was no tenderness on palpation, and the intraocular tension was not elevated. The visual fields were grossly normal. Refraction indicated moderate hyperopic astigmatism, as follows: right eye +2.25 D sph \subset +0.50 D cyl, axis 95, left eye +2.00 D sph \subset +0.50 D cyl, \subset axis 85. Vision was not improved with lenses.

The patient was given polyvitamins and riboflavin. Atropine was instilled in each eye, and hot compresses were applied.

On the day following his admission vision had dropped to 10/200 in each eye and corneal opacities were much more dense. Thereafter there was gradual improvement, with visual acuity of 20/200 on the fourth day and 20/40 on the ninth day after admission. There continued to be some fluctuation in density of the opacities, and after two months vision had not improved beyond 20/30 in each eye and there were residual corneal opacities.

After the first few days of hospitalization the patient began to complain of vague abdominal distress and malaise. General examination and medical consultation revealed nothing of significance at this time. Initial laboratory tests disclosed only moderate secondary anemia, with 3,770,000 red blood cells and 75 per cent hemoglobin, the urine was normal, and the icteric index was 6. The patient was treated symptomatically with tincture of belladonna and phenobarbital, without relief. On December 11 *Necator americanus* was found in the stool, and the patient was given tetrachloroethylene as a vermifuge, subsequent examinations of the stool were negative for the parasite.

By December 21 epigastric distress had become severe, and abdominal distention, ascites and clinical icterus had developed. Treatment included large doses of a preparation of vitamin K and intravenous injections of dextrose, plasma and whole blood.

The patient's general condition seemed somewhat improved, and on Jan 11, 1945 he was transferred to this general hospital. Laboratory tests were then reported as showing 2,450,000 red blood cells, 50 per cent hemoglobin and 3,950 white blood cells. The corrected sedimentation rate was consistently elevated, e.g., 21 to 26 mm in one hour. Determinations of the serum proteins indicated a reversed albumin-globulin ratio, the total proteins measuring 6.6 Gm, with 2.6 Gm of albumin and 4.0 Gm of globulin, per hundred cubic centimeters. Intensive therapy was continued, with repeated blood transfusions and intravenous injections of plasma, 50 per cent dextrose and mereurophylline. The ascites and edema gradually subsided, but by February 2 the icteric index had risen to 170. The patient had recurrent and persistent bleeding from the nose, gums and rectum, and despite supportive treatment there were increasing depression and drowsiness. He finally became stuporous and lost consciousness one day before his death, on February 19. The final clinical diagnosis was "acute hepatitis with jaundice, cause undetermined."

Quinacrine therapy had been discontinued in mid-December, when abdominal complaints became pronounced, at that time vision was 20/30 in each eye, and the residual corneal edema persisted. By Jan 27, 1945 vision had cleared to approximately 20/20 in each eye. Repeated subsequent examinations with the ophthalmoscope and hand slit lamp during this terminal phase of his illness failed to disclose any demonstrable corneal opacities.

Postmortem examination was performed by the pathologist at this hospital, and a complete report was submitted to the Surgeon General. The pathologic diagnoses included (1) diffuse necrosis of the liver, (2) bile nephrosis, (3) splenomegaly (weight, 500 Gm) with hyperemia and hyperplasia of the splenic

pulp, (4) intra-alveolar pulmonary hemorrhage, (5) generalized icterus, and (6) multiple subcutaneous hemorrhages

The following description of the pathologic changes in the liver is quoted in detail from the autopsy report

"The liver weighed 1,750 Gm and measured 28 by 16 by 7 cm. The capsule was pale gray, smooth and translucent. The edges of the liver were sharp. The organ cut with normal resistance and showed a reddish brown, slightly bulging cut surface, in which the central veins of the hepatic lobules stood out prominently as red dots. Microscopic examination of sections taken through the liver revealed that the parenchyma was almost completely destroyed and the normal architecture greatly distorted. Only small groups of hepatic cells remained, and these were widely separated by edematous stroma. The parenchymal cells were undergoing all degrees of degenerative change, from pronounced cloudy swelling to complete necrosis. All the remaining hepatic cells were intensely bile stained. There was edema of the portal areas, but no proliferation of the fibrous connective tissue and only beginning multiplication of the bile ducts. There was no infiltration of inflammatory cells, either in the stroma of the portal areas or in the supporting tissue of the liver. There was hyperemia of the central veins and adjacent capillaries of the portal lobules."

ANALYSIS OF CASES

History—Impaired vision was the only presenting complaint. The blurring was evident at all distances, and there was no apparent restriction of the visual fields, the condition was most troublesome at night, when there was a pronounced dispersal of lights. There was no associated ocular irritation, pain or redness or conjunctival discharge. In none of the cases was there a history of injury to the eyes or of undue exposure to brilliant light, dust or irritants. The diet had apparently been adequate, consisting largely of canned foods. It was found that all the patients had within two months been stationed in the United States or had been on extended leave in New Zealand, where ample fresh fruits, vegetables, meats and dairy products were available.

Each of the 4 men was receiving quinacrine, and this was apparently the only medicament prescribed. Three of them had been taking the drug only four to six weeks prior to the initial visual disturbance. The fourth had taken quinacrine hydrochloride for twenty months, but seven weeks before he first noticed blurring of vision the usual dose of 0.1 Gm had been increased to 0.2 Gm daily.

Ocular Examination—Visual acuity was impaired to about the same degree in the two eyes, as indicated in the individual case reports. On admission these patients showed a diffuse haziness of each cornea. The cornea had a granular appearance, due to innumerable minute punctate opacities evenly dispersed over its surface. Examination with the slit lamp and corneal microscope showed these delicate opacities to be located near the level of Bowman's membrane. There seemed to be increased reluctance of the most superficial layers of the corneal parenchyma, as well as involvement of the deeper epithelial cells. At

that time the epithelial surface was smooth and did not stain with fluorescein. Ophthalmoscope study with a +8.00 D lens revealed the opacities as a fine granular stippling seen in silhouette against the fundus reflex.

There was no injection of the conjunctiva and no evidence of inflammation involving the aqueous, iris, lens, vitreous or fundus. The visual fields were normal in all respects. Repeated tonometric readings of intraocular tension taken at various hours of the day were within normal limits.

General Investigation on Admission—In each case the general history and physical examination on admission disclosed no evidence of systemic disease. Consultations with members of the dental, otolaryngologic and urologic staff revealed no foci of infection. Initial laboratory tests, including complete blood counts and urinalyses, revealed an essentially normal condition, the Kahn reaction of the blood was negative, and smears revealed no malarial organisms. Cutaneous reactions were negative to tuberculin (purified protein derivative) in both dilutions. Patch tests with powdered quinacrine gave a negative reaction.

Course—During the first weeks of hospitalization there seemed to be some improvement without specific treatment. Two of the patients were treated with atropine and hot compresses at another hospital and all received large doses of polyvitamins and riboflavin, without apparent benefit. The residual edema and slight blurring fluctuated in intensity, never completely disappearing. The condition of 3 patients was so much improved that this minimal blurring, with dispersal of lights at night, was not considered a contraindication to discharge from the hospital. In each case the pronounced edema and blurring recurred, necessitating rehospitalization.

INVESTIGATION OF THE QUINACRINE FACTOR

All 4 patients had been receiving quinacrine hydrochloride prior to onset of the visual complaints. Patients 1, 2 and 4 had been under treatment with 0.1 Gm daily for only four to six weeks, patient 3 had been taking 0.1 Gm of quinacrine hydrochloride daily for twelve months, but this dose had been increased to 0.2 Gm daily six weeks prior to the onset of visual complaints. These patients were examined regularly while continuing to receive the usual suppressive dose of 0.1 Gm of the drug daily, they showed variations in density of the residual corneal edema with corresponding fluctuation in visual acuity, but vision never became completely clear and the punctate opacities never entirely disappeared.

The reactions in the patch tests for quinacrine were negative, but no cause for the corneal edema had been determined. In an attempt

completely to rule out toxicity due to quinacrine as a possible factor it was decided (1) to stop the drug completely for one month and (2) to administer larger doses of quinacrine. Only patients 1, 2 and 3 were available for this investigation.

During the period in which no quinacrine was taken there were a slow but definite improvement in the corneal condition and further clearing of the slight visual impairment. However a small amount of edema persisted and there was visual disturbance particularly noticeable in dispersal of lights at night.

These 3 patients were then given the intensive course of quinacrine therapy consisting in administration of 1.2 Gm the first day, 0.8 Gm the second day and 0.4 Gm on each of the succeeding four days. Patients 1 and 2 completed the full course of treatment, but patient 3 was unable to tolerate the drug owing to persistent vomiting. Its administration was finally discontinued on the fourth day. The exact amount of the retained drug could not be determined.

In patients 1 and 2 who completed the full course, there developed pronounced corneal edema beginning six and eight days respectively, after the drug was started. In patient 3, who did not complete the course the blurring and edema began eleven days after the initial large dose of quinacrine. This corneal edema was more intense than had previously been seen in any of these patients, and for the first time there were punctate erosions of surface epithelium. Quinacrine therapy was the only factor in their routine which was altered during this period.

HEPATIC FUNCTION

Impairment of hepatic function was a late occurrence in these patients and in each it became apparent three to six months after the initial episode of visual disturbance. The medical investigation on the patient's admission had shown an essentially normal condition.

Patient 1 had no symptoms suggestive of hepatic dysfunction prior to taking the intensive course of quinacrine treatment. He had some nausea, anorexia, vague abdominal distress and loss of 5 pounds (2.3 Kg) in weight with the larger dose of the drug but showed no enlargement or tenderness of the liver. The icteric index increased to 15, and excretion of hippuric acid dropped to 1.6 Gm in terms of hippuric acid and to 1.1 Gm in terms of benzoic acid. The medical consultant made the diagnosis of 'hepatitis with subclinical icterus and impaired hepatic function as shown by the hippuric acid excretion test'.

Patient 2, likewise had no complaints indicative of impaired hepatic function before the dose of quinacrine hydrochloride was increased. With the intensive course he experienced nausea, vomiting, increasing anorexia, malaise, tenderness in the right upper abdominal quadrant and loss of weight of at least 10 pounds (4.5 Kg). Examination showed

moderate abdominal distention and minimal ascites, with a fluid wave. The liver was enlarged and tender and was palpable 2 fingerbreadths below the costal margin. The corrected sedimentation rate was 26 mm in one hour, the hippuric acid excretion test showed reduction to 1.3 Gm per hundred cubic centimeters in terms of benzoic acid, the icteric index was 12. The medical consultant made the diagnosis of "hepatitis with subclinical icterus."

Patient 3 had vague abdominal complaints for about three months with no objective signs. On receiving larger doses of quinacrine, this patient had persistent vomiting, which necessitated discontinuation of the drug. He then complained of increasing abdominal distention, tenderness in the right upper quadrant, nausea and vomiting. The liver was large and tender, there were definite ascites and clinical icterus. Laboratory tests showed an average icteric index of 40 and total plasma proteins measuring 6.1 Gm, with 2.6 Gm of albumin and 3.5 Gm of globulin, per hundred cubic centimeters. A diagnosis of "severe hepatitis" was made by the medical consultant.

The fourth patient was not given the intensive course of quinacrine therapy. Severe hepatitis with clinical icterus and ascites had already developed before his transfer to this hospital. Laboratory tests revealed icteric indexes as high as 170, a reversed serum albumin globulin ratio, an elevated sedimentation rate and pronounced secondary anemia. Post-mortem examination disclosed extensive diffuse necrosis of the liver.

INCIDENCE OF CORNEAL EDEMA

Corneal edema would seem to be a relatively infrequent manifestation of quinacrine sensitivity. While the symptoms are of such nature as to cause the patient to seek early medical assistance, the diagnosis may not be readily apparent to the untrained observer. The condition of a number of these patients has been initially diagnosed as "dystrophy," particularly when precision equipment was not available.

During the four months since this paper was originally submitted, we have examined 2 more patients with this type of corneal edema. In each of these patients the blurring of vision began a few weeks after he started to take quinacrine. Likewise, as in the original cases, the corneal edema subsided after use of the drug was discontinued. One of these patients was again given quinacrine, and the corneal edema recurred. Initial tests of hepatic function were made in each case and found to be within normal limits. Circumstances made it impossible to carry out a more complete or prolonged investigation of these patients, and for this reason the case reports are not presented in detail.

On the basis of verbal communications to us, it is estimated that at least 25 cases of corneal edema have been recognized in the Pacific

theater These have been distributed through seven general hospitals and a corresponding number of smaller medical units

COMMENT

That quinacrine may precipitate corneal edema in sensitive persons would seem to be clearly indicated

It is of interest that in each of the patients available for prolonged study there apparently developed at least some degree of impairment in hepatic function

During the period in which these patients were observed there was a relatively high incidence of "infectious hepatitis" in the Pacific area in which they were stationed A considerable number of the patients who were hospitalized primarily for hepatic disease were carefully examined, and no instance of corneal edema was found In the interval of eight months during which these studies were carried out there were 65 cases of "infectious hepatitis" in this general hospital, a ratio of about 14 per thousand admissions

In interpreting the associated impairment of hepatic function in these patients with corneal edema, the presence of "infectious hepatitis" in the area must be considered However, since in each of the 4 patients with this unusual form of corneal edema precipitated by quinacrine hepatic dysfunction also developed, the possibility that quinacrine might likewise be a contributing factor in the hepatic disease should be given further investigation

SUMMARY

Four cases of bilateral superficial corneal edema are presented in detail

Visual impairment was the only initial complaint This blurring was of approximately the same degree in the two eyes, fluctuated in severity and was most noticeable with the dispersal of lights at night

Each patient had been taking protective doses of quinacrine Three had received the drug for only four to six weeks before the initial visual disturbance One had been taking 0.1 Gm of quinacrine hydrochloride for twelve months but had had the dose increased to 0.2 Gm seven weeks prior to onset of blurring

Visual acuity was variable, and in 1 instance vision dropped to 10/200 in each eye Examination showed diffuse haziness of the corneas due to evenly dispersed punctate, superficial opacities These opacities were located primarily in the superficial layers of the cornea, but on initial examinations the epithelial surface was smooth and did not stain with fluorescein There was no evidence of ocular disease, and the general medical investigation on admission showed no systemic disease The corneal edema and blurring of vision fluctuated in severity

while the patient was still receiving 0.1 Gm of quinacrine hydrochloride, but the opacities never disappeared. Patch tests gave negative reactions for quinacrine.

Quinacrine was withheld from 3 patients for one month, and there was definite clearing of residual opacities. The patients were given large doses of the drug and exhibited pronounced corneal edema, beginning six to eleven days after the first large dose of quinacrine. This was similar to the edema previously observed, but generally more severe, and there was punctate staining of the surface epithelium. Quinacrine therapy was then permanently discontinued, and edema gradually subsided. At the end of one month vision with correction was approximately 20/20 in all cases. After eight weeks there were no demonstrable opacities in 2 cases, and in the third case only an occasional punctate opacity could be detected.

In each of these 4 cases of corneal edema some degree of hepatic dysfunction subsequently developed, beginning three to six months after the initial visual disturbance. In 2 cases there were subclinical icterus and impaired hepatic function, as shown by the hippuric acid excretion test, in the other 2 cases severe hepatitis developed, terminating fatally in 1 case.

We have made examination in 2 additional cases of corneal edema since the original reports were submitted. On the basis of verbal communications, it is estimated that at least 25 cases of this type of corneal edema have been seen in the Pacific area.

CONCLUSIONS

Quinacrine may precipitate corneal edema in the occasional sensitive person. This may occur with the minimal, 0.10 Gm, daily dose of the drug. A period of several weeks may intervene between the first dose of the drug and the initial visual disturbance. When larger doses of quinacrine are employed, this interval of lag may be reduced to a few days.

Further investigation of hepatic function is indicated in these patients with corneal edema precipitated by quinacrine.

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RETURN OF VISION IN TRANSPLANTED ADULT SALAMANDER EYES AFTER SEVEN DAYS OF REFRIGERATION

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NUMEROUS experiments on various types of salamanders, both larvae and adults, have shown that when the eye is grafted in the orbit immediately after it has been excised the transplant in most cases eventually recovers its visual function (Stone and associates¹). In some of these experiments eyes of animals of different species were exchanged. The success of the experiments, indicated by return of vision, was due not only to an early revascularization of the grafted eye and the preservation of its essential tissues but to the capacity of regeneration possessed by these eyes.

However, the picture of regeneration in the grafted eyes of larvae was quite different from that in the transplanted eyes of adults. In the larvae (Stone^{1a}, Stone, Ussher and Beers^{1b}) all the parts of the grafted eye survive except for occasional loss of a few ganglion cells in the retina. The optic nerve could therefore regenerate rather rapidly from the severed stump connected with the retina. In the transplanted adult eye the retinal tissue degenerates rapidly with the exception of a peripheral ring of cells which survives along the ciliary margin. From these cells a new retina regenerates, and when differentiation is completed a new optic nerve emerges and passes along the pathway of the old degenerated

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1 (a) Stone, L. S. Heteroplastic Transplantations of the Eyes Between Larvae of Two Species of *Amblystoma*, *J. Exper. Zool.* **55** 193-261, 1930. (b) Stone, L. S., Ussher, N. T., and Beers, D. N. Reimplantation and Transplantation of Larval Eyes in the Salamander (*Amblystoma punctatum*), *ibid.* **77** 13-48, 1937. (c) Stone, L. S., and Zaur, I. S. Reimplantation and Transplantation of the Adult Eyes in the Salamander (*Triturus viridescens*) with Return of Vision, *ibid.* **85** 243-269, 1940. (d) Stone, L. S., and Ellison, F. S. Exchange of Eyes Between Adult Hosts of *Amblystoma punctatum* and *Triturus viridescens*, *Proc. Soc. Exper. Biol. & Med.* **45** 181-182, 1940. (e) Stone, L. S., and Cole, C. H. Grafted Eyes of Young and Old Adult Salamanders (*Amblystoma punctatum*) Showing Return of Vision, *Yale J. Biol. & Med.* **15** 735-754, 1943. (f) Stone, L. S. Functional Polarization in Retinal Development and Its Reestablishment in Regenerating Retinae of Rotated Grafted Eyes, *Proc. Soc. Exper. Biol. & Med.* **57** 13-14, 1944.

nerve The degeneration of the retina is initiated by a temporary loss of blood supply (Stone and Chace²) The reformation of a new retina can be brought about several times, as shown by Stone and Farthing,³ who recorded that return of vision could be demonstrated four times in the same eye repeatedly transplanted

In all the experiments just described the eyes were grafted to freshly denuded orbits in new hosts immediately after they had been removed from the donors In 2 cases, however, described by Stone and Farthing³ (pages 277 to 278), there was some delay before the transplanted eyes were finally attached to living hosts When the eyes were being grafted for the third time the animals which were to have been the hosts for that period failed to revive from the anesthesia Twenty-four to thirty-six hours after the operation the hosts were dead The eyes, which had not yet shown prominent gross changes of degeneration, were immediately grafted to new hosts Since they survived and were finally carried successfully through the four stages of transplantation, further experiments were devised to test the capacity of the adult eye of the salamander used to recover after it had been isolated from its blood supply for a long period before transplantation To preserve the tissues in the graft during this period, the eyes were kept under refrigeration at various temperatures The present paper will give a detailed account of the observations, some of which have appeared in a preliminary report (Stone⁴)

MATERIAL AND METHODS

Right and left eyes of adult salamanders (the vermilion spotted newt, *Triturus viridescens*) were carefully excised under the compound dissecting microscope in a manner already described by Stone and Zaur^{1c} and placed in dishes on filter paper moistened with sterile Ringer solution The dishes were then placed in a refrigerator under temperatures varying from 0 to 8 C, where they were left for periods of from two to fourteen days Special care was taken to orient each eye on the filter paper to preserve the identity of all poles of the eye, so that later the graft could be normally oriented in the new host

When the eye was transplanted, the right or the left eye, according to the demands of normal orientation, was excised from a new host, and into the freshly denuded orbit the refrigerated graft was placed in the normal orientation The hosts were then placed on wet filter paper in cool chambers, where they remained quiet for twenty-four to thirty-six hours, during which time the eye healed sufficiently in place without the use of sutures The animals were then placed

2 Stone, L S, and Chace, R R Experimental Studies on the Regenerating Lens and the Eye in Adult *Triturus Viridescens*, *Anat Rec* **79** 333-348, 1941.

3 Stone, L S, and Farthing, T E Return of Vision Four Times in the Same Adult Salamander Eye (*Triturus Viridescens*) Repeatedly Transplanted, *J Exper Zool* **91** 265-285, 1942

4 Stone, L S Return of Vision in Transplanted Adult Salamander Eyes After Several Days of Refrigeration, *Proc Soc Exper Biol & Med* **54** 44-45, 1943

in water in separate aquariums, where they could be examined daily and records kept of the condition of the graft. A report will be given of the results of 70 experiments.

OBSERVATIONS

Delay Two Days, Temperature 8 C—In 6 cases the right eye grafts were refrigerated for two days at 8 C before they were transplanted. At the time these eyes were grafted their gross appearance had not changed much from that at the time they were enucleated. Ten days after the eyes were grafted the cornea in all cases was clear. The pupil was much contracted, and the pattern of iris pigmentation was changing. The normal sharp black band (fig 1) had become less distinct, and the yellow portion of the iris was darker. The lens was degenerating. The appearance was similar to that of an eye sixteen to twenty-one days after it had been immediately grafted, without delay, as shown by Stone and Zaur^{1c}. Slow circulation had begun to appear in some of these eyes. It is obvious that the initial degenerative changes in the grafted eyes had progressed more rapidly after the delay in transplantation.

Within three months 3 eyes had slowly become resorbed until they were small corneoscleral sacs, 1 of which still showed a small amount of black pigment through a thickened, but clear, portion of the cornea. Three eyes at the end of fifty days gave an appearance similar to that of grafted eyes shown by Stone and Zaur^{1c} thirty to forty days after operation, indicating that the recovery of these eyes was retarded about two weeks, as compared with eyes transplanted without delay. In about three months these eyes had regained their normal appearance except for a reduction in size. At this time the normal (left) control eye was removed, and return of vision in the grafts was proved by the methods described previously (Stone and Zaur^{1c}).

The gross appearance of these eyes is indicated in a photograph (fig 2) taken one hundred and two days after operation. The appearance of the regenerated retina and its similarity to the normal (4) are shown in 5 of the figure. It is therefore obvious that some eyes can be kept as long as two days at a temperature of 8 C and be successfully grafted.

Delay Three Days, Temperature 4 to 6 C and 8 C—In 5 cases right eyes were refrigerated for three days at a temperature of 8 C before they were grafted. At this time the eyes were still clear, but the luster and color of the iris were not so brilliant as at the time of excision. Nine days after transplantation the cornea in all the grafts was becoming cloudy. The iris had darkened in most grafts, indicating rapid changes in the eyes. In fifty days 3 eyes had become small, darkly pigmented spheres with slightly cloudy corneas. Two other eyes at this time had not degenerated to the same degree. The corneas were clear. However,

the eyes slowly degenerated to small sacs by the end of four months. The other 3 eyes had reached this stage by the end of the third month. Therefore none recovered which had been refrigerated at 8 C for three days.

In 5 other cases the eyes were kept for three days at a lower temperature, approximately 4 to 6 C. At the time they were grafted their gross appearance was about the same as that of the eyes which had remained for three days at a temperature of 8 C. At the end of ten days after transplantation the cornea was clear in all eyes and slow circulation was observed. In forty days the recovery of 2 grafts appeared similar to that of eyes which have been transplanted immediately after enucleation (Stone and Zaur^{1c}). The other 3 grafts were smaller and gave the appearance of slower recovery. Unfortunately, 2 of the hosts escaped twenty-two days later, before the eyes had fully recovered for visual tests. The 3 surviving hosts showed large, normal-appearing eyes. One of the eyes, the slowest to recover, was about four fifths of the normal size. The normal (left) control eyes of these hosts were removed at this time and visual tests showed that normal function had returned in the 3 cases. Two animals were killed one hundred and eight days after operation, and the appearance of the retina is indicated in 6. Therefore a delay of three days before transplantation demands a temperature below 8 C (about 4 to 6 C) to bring about a successful result.

Delay Four Days, Temperature 0 C, 4 to 6 C and 8 C—Five right eyes were refrigerated four days at a temperature of 8 C. At the time they were grafted the yellow pigment in the iris was pale. The corneas and lenses were clear. The bulbs were not so firm as at the time of excision. At the end of a week after transplantation there were varying degrees of cloudiness in the corneas. In 2 cases the iris had sunken inward over a cloudy lens. In only 1 case did red spots in the iris indicate living red blood cells in loops of blood vessels. No circulation was observed. By the forty-fifth day 3 grafts were small, round, opaque, pigmented balls. Two eyes at this time were not so extensively degenerated. The corneas were clear. The iris was darkly pigmented and sunken. In three months 4 specimens were small white spheres with indications of varying amounts of centrally placed black pigment. One of the eyes was small with a thick, semitransparent cornea, through which one could see a black pigmented membrane with a large central opening. There was some golden pigment in the ventral portion of this iris. Since one could see a nonpigmented, pinkish background through the central opening, it was evident that the retinal area was permanently lost. Twenty-two days later this eye was almost completely resorbed.

In 2 cases a right and a left eye were left for four days at freezing temperature (0 C). They were thawed in Ringer solution before graft-

ing At this time the cornea and lens were clear The iris was pale and sunken, and the pupil was distorted These eyes never recovered but were rapidly resorbed, until by two months they were mere small white corneoscleral sacs

In another group 5 right and 5 left eyes were excised, washed in sterile Ringer solution in the usual manner and, under sterile conditions, placed under refrigeration at a temperature of from 4 to 6 C During the second day the thermal control to the ice box had failed to function for several hours before the trouble was discovered At this time the temperature of the compartment in which the eyes were kept had risen above 10 C The eyes were removed and placed under new sterile conditions, and the desired temperature was soon reinstated for the remainder of the four day period

At the time the eyes were grafted 3 left eyes were discarded, since they were soft and partially collapsed The remaining 7 were transplanted, although some of them appeared less firm and all were subnormal in appearance All but 1 of these eyes were slowly being reduced to small sacs during the first month In the exceptional case, although the graft gradually became smaller, it was on the sixty-ninth day, at the time of fixation, a small eye with a thickened, clear cornea, through which one could see black and yellow iris pigment, not arranged in the normal pattern which is so common in a fully recovered grafted eye The pupil was maximally contracted Circulation was rapid in the blood vessels of the iris Histologically, the appearance of the eye was similar to that shown in 7 of the figure The case was one of an eye undergoing slow resorption without sufficient surviving cells to insure its full recovery In the light of other experiments later reported in this paper, it is obvious that the temporary rise in temperature above the intended refrigeration level of 4 to 6 C accounted largely for the end results in this group of grafts

Delay Five and Six Days, Temperature 4 to 6 C and 8 C—At the temperature of 8 C 6 eyes were kept for five days and 5 eyes for six days before they were grafted After refrigeration the eyes appeared soft The iris was less brilliant, and occasionally loose pigment cells were seen between the cornea and the iris At the end of a week after transplantation 3 of the eyes refrigerated for five days showed areas of the cornea sloughing All of the eyes refrigerated for six days showed the same condition at this time These eyes rapidly collapsed, and what remained was resorbed during the first month The 3 eyes kept for five days which did not collapse during the first two weeks after transplantation were resorbed less rapidly, for at the end of a month they were small corneoscleral sacs, some of which contained small amounts of pigment

In another group, 6 left eyes were kept for six days at a lower temperature (4 to 6 C) before they were grafted. At the time the eyes of this group were transplanted they showed less damage than the eyes kept for five and six days at the higher temperature (8 C). All these eyes healed and recovered circulation. At eighteen days 2 of them were reduced to one-half their original size, and by the end of a month they were small, flattened, pigmented sacs, being rapidly resorbed. Histologic examination of 1 of them showed a small corneoscleral sac filled with a mass of pigment and scattered groups of iris cells which had survived. The remaining 4 grafts were being resorbed at a much slower rate. Two of them were preserved for histologic study on the thirty-fifth day. Both were small eyes with thick corneas. In 1 eye the retina, which had attempted regeneration, was an uneven, solid wall of undifferentiated cells and with the slender iris formed a small cup surrounded by heavy choroid pigment. A small lentoid mass was embedded in the dorsal portion of the iris. In the center was a small spherical remnant of the original lens not yet completely degenerated. It was surrounded by a film of pigment cells. The other eye showed a better attempt at regeneration, although it was also very small. The retina was thicker, and limited regions showed differentiation of retinal layers. The original lens had completely disappeared, and a new but small one had regenerated from the dorsal part of the iris, similar to the lens shown in 7. There was no attempt to form an optic nerve in either case.

The 2 remaining eyes were kept under observation for sixty-four days because at the end of the first month there was indication these eyes might make a good attempt at recovery. However, at the end of two months 1 eye became rather small. The condition is shown in 7 and is typical of an eye undergoing slow resorption in which a portion of the retina had attempted regeneration. A small lens had also regenerated from the dorsal pupillary margin of the iris. The larger of the 2 eyes possessed a new lens of greater size. Much of the retina had reached a considerable degree of regeneration and differentiation. The central part was greatly retarded, owing to a rupture in the wall of the eyeball.

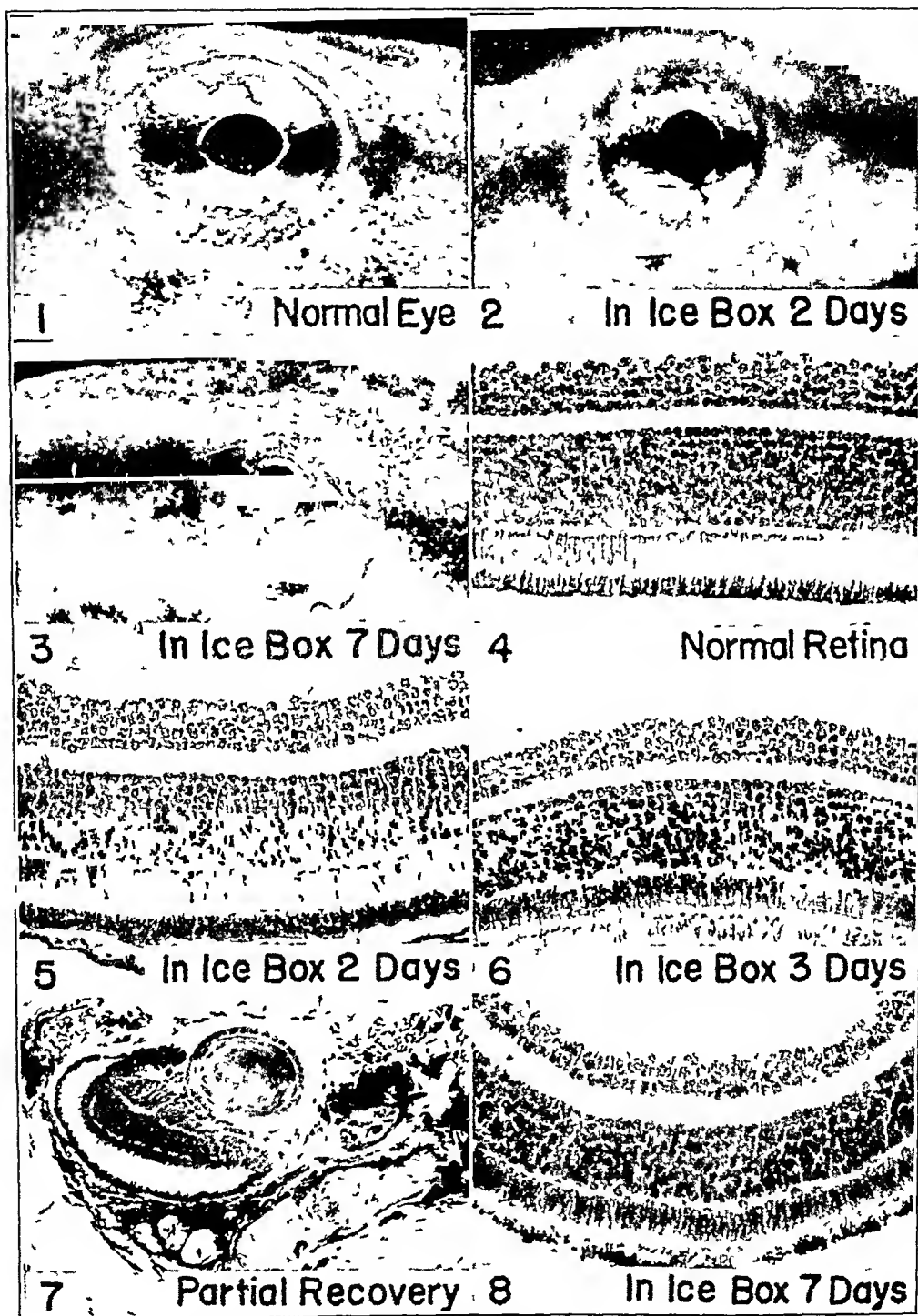
Delay Seven to Fourteen Days, Temperature 0 C , 4 to 6 C and 8 C.—Eight eyes were kept for seven days and 2 eyes for eight days at freezing temperature. At the time they were grafted most of them were clear and in good condition. Only 1 eye had a slightly opaque lens and cornea. The gross appearance was deceiving, for by the end of a week most of the grafts were rapidly degenerating. In some eyes portions of the cornea and iris were sloughing. Although 2 eyes were kept over two months, because the corneas remained clear for a long period, there was no ability in any of these eyes to combat the steady degeneration which overtook them.

Since better results were obtained when eyes were kept at a temperature of from 4 to 6 C, an attempt was made to refrigerate 6 left eyes for a period of seven days at that temperature before they were grafted. When they were taken from the ice box, the corneas and lenses in all cases were clear. Two eyes showed a yellow fringe of iris cells, which had wandered inward from the pupillary margin. A brownian movement of pigment granules indicated that some cells had disintegrated. All other eyes showed a smooth, bright, clear iris, with not quite the same luster as the normal eye.

By the twenty-fourth day after transplantation 4 grafts had become smaller. In 2 of them the cornea was becoming opaque. In all 4 eyes the iris was sunken, although circulation was present. These 4 eyes were undergoing resorption. In 2 other grafts, however, the eyes were only slightly smaller than normal and gave good evidence that no extensive degeneration was taking place, as in the 4 grafts just mentioned.

At the end of seventy-one days the pigment pattern was returning in the iris of these eyes. A new lens was regenerating. The grafts were recovering, but at a slower rate than eyes which are transplanted immediately after enucleation. At one hundred and twelve days the normal (right) eyes of these hosts were removed so that tests for vision could be made on the grafts. The eyes, with the exception of a slight reduction in size, were normal in appearance. About a week later they were tested for vision. Vigorous and sharp normal visual responses to a moving lure were clearly demonstrated. The hosts of these eyes were kept for three hundred and sixty-six days. At the end of this time the grafts were still large, beautiful, normal-functioning eyes. A motion picture record was made of 1 of these eyes. Its appearance at this time is shown in 3 of the figure. The regenerated retina is also shown in 8.

It appears from these experiments that the best survival of grafts is obtained when the eyes are maintained at a temperature from 4 to 6 C if delay is intended before they are transplanted. Therefore an attempt was made to delay transplantation for a period longer than seven days when eyes were refrigerated at this temperature. Four left eyes were kept at this temperature for fourteen days before they were grafted. They were briefly examined at various periods while under refrigeration. After the first week in the ice box epithelial cells tended to scale loose in some places on the surface of the cornea. After eight to ten days the lenses did not appear as clear as formerly. When the eye was grafted on the fourteenth day of refrigeration, the iris was smooth but less brilliant. There were no loose cells. The corneas were clear, but the lenses were slightly opaque. The eyes were soft, and 1 was broken in an attempt to graft it. After two days 1 eye was clear. The cornea in another eye was rather opaque. Two eyes had sloughed and broken down completely.



(See legend on opposite page)

The 2 eyes which did not disintegrate early were small, opaque corneo-scleral sacs in twenty-one days, showing a rapid resorption of the degenerating tissue of the eye. Histologically examination of 1 of them revealed an extensive invasion of blood vessels among scattered clumps of pigment and isolated fragments of the iris.

CONCLUSIONS AND SUMMARY

From the results of these experiments it is clear that a period of refrigeration for the isolated adult eye of this species much longer than seven days does not preserve the eye sufficiently for successful transplantation. Perhaps with a great many experiments it might be shown that the time could be extended a day or two in obtaining a successful result. It is not unexpected that the cornea has considerable survival capacity and may remain clear for a long time. This is expressed somewhat for vertebrates in general by the fact that corneal banks are now established for transplants in human eyes. However, considering the fact that when the adult eye of this salamander is transplanted a new lens regenerates from the dorsal pupillary margin of the iris and a new retina regenerates from the undegenerated ciliary margin of the old retina, it is remarkable that cells which replace these highly differentiated parts of the eye can survive so well for as long as seven days under refrigeration.

These experiments can be summarized in the following statements:

Seventy enucleated eyes of the adult salamander (the common vermilion spotted newt, *Triturus viridescens*) were refrigerated at a tem-

EXPLANATION OF PLATE

- 1, normal adult eye of *Triturus viridescens*, $\times 8$
- 2, eye one hundred and two days after transplantation, $\times 8$. Refrigeration at a temperature of 8 C was maintained for two days. Visual function was demonstrated.
- 3, eye three hundred and sixty-six days after transplantation, $\times 8$. Refrigeration at a temperature of 4 to 6 C was continued for seven days. Visual function was demonstrated one hundred and nineteen days after transplantation.
- 4, photomicrograph of a section of the normal retina of the adult eye of *Triturus viridescens*, $\times 130$
- 5, photomicrograph of a section of the retina of a functional eye one hundred and two days after transplantation, $\times 130$. Refrigeration had been continued for two days at a temperature of 8 C.
- 6, photomicrograph of a section of the retina of a functional eye one hundred and four days after transplantation, $\times 130$. Refrigeration had been continued for three days at a temperature of 4 to 6 C.
- 7, photomicrograph of a section of a partially resorbed eye sixty-four days after transplantation, $\times 65$. Limited regeneration of the retina and lens is indicated. Refrigeration had been continued for six days at a temperature of from 4 to 6 C.
- 8, photomicrograph of a section of the retina of a functional eye (that shown in 3) three hundred and sixty-six days after transplantation, $\times 130$. Refrigeration had been continued for seven days at a temperature of from 4 to 6 C.

perature of from 0 to 8 C in sterile Ringer solution for periods ranging from two to fourteen days and were then transplanted into freshly denuded orbits of new hosts. Right and left eyes were grafted and normally oriented.

When the eyes were kept under freezing conditions (0 C), the grafts eventually degenerated, the rapidity with which they succumbed depending partially on the time they had remained under refrigeration.

After two days of refrigeration at 8 C the success of the grafts is expressed by the fact that in some cases the eye eventually became a normal-appearing normally functioning organ again.

Refrigeration for longer than two days required a lower temperature (4 to 6 C.) to insure survival of the graft and successful transplantation. Eyes isolated as long as seven days at this temperature were successfully grafted, and return of vision was demonstrated a little over three months after they were transplanted. These eyes remained functional and were normal in appearance one year after they were grafted. At this time the hosts were killed for microscopic studies. A motion picture record was obtained of these experiments.

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OCULAR DERMATITIS FROM LOCAL PENICILLIN

Report of Two Cases

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SINCE the clinical introduction of penicillin by Abraham and associates¹ for the treatment of systemic and local infections, the serious toxic manifestations of this drug have been remarkably few. Keefer and associates² encountered relatively mild untoward reactions in 69 (13.8 per cent) of their series of 500 patients treated systemically with penicillin. Of this group, urticaria occurred in 14 patients, chills and fever in 17 and localized thrombophlebitis in 19. All the reactions were transitory and did not require cessation of the drug therapy. Sensitivity to penicillin was not evident, even though several patients had repeated prolonged courses. Lyons³ reported that urticaria was the most common complication in his group, occurring in 5.7 per cent of the 209 patients treated systemically with penicillin. He attributed these reactions to toxic impurities rather than to the active penicillin fraction. He found that thrombophlebitis, which often occurred at the site of the intravenous injection, could be avoided by frequent change in the position of the needle. Herrell and associates⁴ noted 2 cases of cutaneous sensitivity in their series of 150 patients treated parenterally with penicillin. They cautioned against the continued use of this drug in the presence of a generalized cutaneous reaction because of the possibility of development of exfoliative dermatitis.

The ready diffusibility of penicillin and its remarkable bacteriostatic power against sensitive staphylococci and streptococci, even in the presence of purulent secretion, are rapidly establishing this drug as a most effective therapeutic agent in the local treatment of external ocular

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2 Keefer, C. S., Blake, F. G., Marshall, E. K., Jr., Lockwood, J. S., and Wood, W. B., Jr. Penicillin in the Treatment of Infections. A Report of Five Hundred Cases, *J. A. M. A.* **122** 1217 (Aug 28) 1943.

3 Lyons, C. Penicillin Therapy of Surgical Infections in the U. S. Army. A Report, *J. A. M. A.* **123** 1007 (Dec 18) 1943.

4 Herrell, W. A., Nichols, D. R., and Hillman, D. H. Penicillin, *J. A. M. A.* **125** 1003 (Aug 12) 1944.

diseases. Despite the recent great increase in the clinical use of penicillin for this purpose, reports regarding its hypersensitive reactions have thus far been meager. Florey and Florey⁵ noted no toxic effects in local treatment of 172 patients with penicillin, 89 of them having ocular infections. The drug was instilled at frequent intervals in a petrolatum ointment or in distilled water in a strength of 400 to 800 Oxford units per gram or cubic centimeter. Cashell⁶ reported no untoward reactions in his series of 57 cases of infections of the eye treated locally with penicillin. Bellows,⁷ on the other hand, noted 4 instances of ocular hypersensitization in 46 cases in which topical treatment with penicillin was employed. A severe ocular dermatitis, associated with fever and malaise, was reported by Keyes⁸ after instillation of 4 drops of a saline solution of sodium penicillin containing 1,000 units per cubic centimeter in each eye. Pyle and Rattner⁹ reported a case of contact dermatitis resulting from penicillin, with a positive reaction to the patch test. Further analysis of the drug proved that the pure penicillin, not the medium, produced the allergic reaction.

The following 2 cases of ocular dermatitis due to local application of penicillin are reported because of the apparent infrequency of the condition and for the purpose of stimulating further observation of such reactions. They occurred in a series of 52 cases of external infections of the eye treated at this clinic with sodium penicillin in saline solution or ointment, the strength varying from 500 to 3,000 Oxford units per cubic centimeter or gram. The results of this study will be reported subsequently.

REPORT OF CASES

CASE 1—A soldier aged 25 was admitted to the hospital on Jan 15, 1945 because of redness and irritation of both eyes, which he had noticed during the past two months. Treatment of this condition at a local dispensary had produced no appreciable improvement. His left eye had been practically blind since the age of 3, the loss of vision following a severe ulceration of the cornea.

Physical examination revealed an essentially normal condition except for his eyes. Vision was 20/20 in the right eye and was limited to ability to count

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6 Cashell, G. T. W. Treatment of Ocular Infections with Penicillin, *Brit M J* **1** 420 (March 25) 1944.

7 Bellows, J. G. Penicillin Therapy in Ocular Infections, *Am J Ophth* **27** 1206 (Nov) 1944.

8 Keyes, J. E. L. Penicillin in Ophthalmology, *J A M A* **126** 610 (Nov 4) 1944.

9 Pyle, H. D., and Rattner, H. Contact Dermatitis from Penicillin, *J A M A* **125** 903 (July 29) 1944.

fingers at 1 foot (30 cm) in the left eye. A moderate injection of the conjunctiva was present in both eyes, being especially noticeable in the lower palpebral portions. This was associated with mild crusting blepharitis. The entire pupillary portion of the left cornea was densely scarred throughout its substance and contained deep vascularization. Neither cornea stained with fluorescein. A smear of material from the conjunctiva showed no organisms. A culture of the conjunctival secretion, however, revealed colonies of the beta hemolytic streptococcus.

Treatment with penicillin, in a strength of 1,500 Oxford units dissolved in each cubic centimeter of isotonic solution of sodium chloride, was begun January 19. Two drops of this solution was instilled in each conjunctival sac every two hours during the waking portion of the day. Penicillin of similar strength was also applied to the eyes in a modified white ointment U S P¹⁰ each evening before retiring. A favorable therapeutic response was noted after six days of this regimen, at which time no organisms could be found on culture. The penicillin drops were then instilled at intervals of four hours. On January 27 a mild dermatitis of the eyelids was noted, associated with a slight injection of the conjunctiva. All penicillin therapy was stopped, and the reaction subsided on



Fig 1 (case 1)—Ocular dermatitis, showing acute allergic reaction to penicillin

the following day. Treatment with penicillin was resumed on January 29, and after the third instillation a severe ocular dermatitis of both eyes rapidly appeared (fig 1). The clinical picture closely resembled an acute dermatitis due to atropine. All the eyelids were extremely red and edematous, and their skin was eczematous and weeping, especially of the lower lids. The bulbar and palpebral conjunctiva of both eyes was congested, and a seromucoid secretion was evident along the margins of the lower lids.

After the prompt cessation of penicillin therapy, the acute allergic reaction gradually subsided, disappearing in four days. Marked scaliness of the skin of the lids, however, appeared at this time, associated with moderate wrinkling and itching, which persisted till February 8, a period of five days. After the complete disappearance of the ocular dermatitis, a provocative test with 1 drop of penicillin in saline solution in a strength of 250 units per cubic centimeter promptly produced the reappearance of symptoms, though less severe, when instilled into the eye. No history of allergy could be elicited from the patient.

¹⁰ White wax, 3 per cent, hydrous wool fat, 8 per cent, and petrolatum, 89 per cent.

The patch test gave a negative reaction for penicillin. The cutaneous reaction, however, was strongly positive for the drug.

The patient was returned to light duty and was cautioned to avoid penicillin therapy in the future.

CASE 2—A soldier aged 36 was referred to the eye clinic of the station hospital on Feb 5, 1945 as an outpatient because of redness and discomfort which had been present in both eyes during the past five days. Vision was 20/20 in each eye. Ophthalmic examination revealed evidence of acute bilateral conjunctivitis. The cornea did not stain with fluorescein. A conjunctival smear revealed no organisms. Culture of the conjunctival secretion, however, revealed a beta hemolytic streptococcus.

The following morning the patient was issued a saline solution of penicillin containing 2,000 units per cubic centimeter and was advised to instil 2 drops in each eye every two hours of the waking day. The solution was to be kept in the



Fig 2 (case 2)—Ocular dermatitis from the use of penicillin, involving the lower lids and the cheeks.

refrigerator when not in use. A pronounced improvement was noted seventy-two hours later, both subjectively and objectively. No organisms were obtained from culture at that time. On February 10, after he had used penicillin four days, a small red, vesicular area of dermatitis was noted on the right lower lid and the upper portion of the face. This lesion spread during the next twenty-four hours over the bridge of the nose, similarly involving the left side of the face and the lower lid and assuming the shape of a butterfly (fig 2). The conjunctiva was not involved. The reactions of both the patch and the cutaneous tests were positive for penicillin. The dermatitis gradually resolved and completely disappeared five days after cessation of use of the drug.

COMMENT AND SUMMARY

Two cases of ocular dermatitis due to local instillation of penicillin are described. In the first case the condition resembled acute dermatitis due to atropine, while in the second case it simulated contact dermatitis. The allergic reactions gradually subsided with cessation of treatment with the drug.

As local application penicillin becomes more general in treatment of external diseases of the eye, hypersensitive reactions of this type assume greater clinical significance. The spectacular results frequently obtained with this drug in such cases may be tempered by the allergic manifestations of susceptible persons. In view of this possibility, further observation is necessary to determine whether this form of penicillin therapy should be limited to the external ocular infections which have resisted ordinary therapeutic measures. In these instances, preliminary patch and cutaneous tests of the drug may be advisable, in addition to culturing the organism and determining its sensitivity.

The relationship between these topical allergic phenomena and the systemic reactions due to penicillin given parenterally requires further clinical and experimental investigation for proper evaluation.

CONGENITAL MALFORMATIONS INDUCED IN RATS BY MATERNAL VITAMIN A DEFICIENCY

I Defects of the Eye

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AND

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CINCINNATI

ALTHOUGH congenital blindness of the offspring of poorly nourished animals has often been described, the early reports were specific neither in the analysis of the nutritional deficiency nor in the description of the ocular defects. Most of the observations were made on cattle, and Moore, Huffman and Duncan¹ have reviewed the literature pertaining to this field. Two types of congenital blindness can be distinguished "the true vitamin A type," which is obviously a severe form of xerophthalmia,² and another type which is associated with constriction of the optic foramen.³ The latter, characterized by a dilated pupil and absence of inflammation of the external structures of the eye, is due to atrophy of the optic nerve caused by its passage through the optic foramen, apparently because of bony pressure.¹ It was difficult to attribute this congenital ocular defect to maternal vitamin A deficiency until Wolbach and Bessey⁴ demonstrated that the neural lesions of vitamin A deficiency are caused by a disproportionate growth of the central nervous system in relation to the surrounding bone. Constriction

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From the Children's Hospital Research Foundation, Department of Pediatrics, University of Cincinnati College of Medicine

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4 Wolbach, S B , and Bessey, O A Vitamin A Deficiency and the Nervous System, Arch Path **32** 689 (Nov) 1941

tion of the optic foramen can now be considered a "true" manifestation of vitamin A deficiency. Davis and Madsen⁵ made quantitative studies of carotene intake of cattle and of plasma levels of carotene and vitamin A during pregnancy in heifers who gave birth to weak and blind calves. They found that heifers receiving 30 and 45 micrograms of carotene remained apparently normal but gave birth to defective calves.

The manifestations of prenatal vitamin A deficiency in pigs described by Hale⁶ were of an entirely different character. This investigator fed gilts of known stocks a diet deficient in vitamin A and possibly in other nutritional factors. Owing to anophthalmos or microphthalmos, the offspring were blind. They also showed other malformations, such as accessory ears, cleft palate and harelip, subcutaneous cysts and misplaced kidneys. Hale proved the nutritional origin of these malformations by preventing them when the experimental diet was supplemented with cod liver oil or green fodder. He also proved that genetic factors could be ruled out as the cause of the malformations, since matings of abnormal sons to their mothers or of abnormal brothers to their abnormal sisters resulted in normal offspring if the females were fed an adequate diet during pregnancy.

Reproduction on diets deficient in vitamin A has been thoroughly studied in the rat,⁷ particularly by Mason,^{2a} who described fetal death, prolonged gestation and difficult parturition but not congenital malformations of the offspring. Cannon⁸ attempted to induce malformations in the offspring of female rats which were depleted in vitamin A. He observed sterility, premature resorption of the fetuses, stillbirths and prolonged gestation. However, no congenital malformations were induced.

In 1944 we⁹ reported the appearance of congenital malformations in the offspring of female rats that were depleted of vitamin A. The depletion of the mothers was achieved by placing female rats of the Sprague-Dawley strain for approximately three months after weaning on a preparatory diet (diet U) which had the following percentage

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composition ground whole wheat, 74, crude casein (Casein Company of America), 15, brewers' yeast (Mead Johnson and Company), 10, sodium chloride C P, 1 This diet was supplemented with 60 U S P units of vitamin D (Drisdol, Winthrop Chemical Company) and 4 micrograms of carotene (S M A Corporation) in cottonseed oil every tenth day The small amount of carotene was added to allow growth and maturation to proceed, without storage of vitamin A During this preparatory period about 10 Gm of frozen ground horse muscle without bones was given weekly to each rat to promote growth

When the female rats reached a weight of 150 to 160 Gm and regular estrus cycles were established, they were placed on the purified diet (diet W) and bred immediately to males of the same strain which had been reared on an adequate diet

The purified diet (diet W), which was completely free of vitamin A, had the following percentage composition sucrose, 68, vitamin test casein, 18, vegetable oil, 10, and salt mixture 4¹⁰, 100 Gm of this diet was supplemented with 0.8 mg of thiamine hydrochloride, 0.8 mg of pyridoxine hydrochloride, 0.8 mg of riboflavin, 1 mg of calcium pantothenate, 10 mg of nicotinamide and 100 mg of choline chloride Every tenth day preparations of vitamin D (1 drop of a 1:4 dilution of Drisdol in olive oil), vitamin E (1 drop of a solution of 5 Gm of alphatocopherol in 100 cc of olive oil) and a vitamin K analogue (1 drop of a solution of 1 mg of menadione in 5 cc of olive oil) were also given

A daily vaginal smear was made from each mature female in order to confirm breeding by the finding of sperm and to watch for signs of beginning resorption Loss of weight and profuse vaginal bleeding were considered to mean interruption of pregnancy The profuse bleeding of resorption must be distinguished from the normal blood sign, which appears between the tenth and the fifteenth day and which consists of a small amount of blood in the vaginal smear In case of interruption of pregnancy the animals were opened and the fetuses removed and examined When the young were carried to term, the mothers were opened on the twenty-second day of gestation No attempt was made to keep alive the young thus removed

One hundred and forty females were raised and bred in this manner, and in 96 of them sperm were found Neither fetuses nor young were obtained from 60 females which died before the fourteenth day of gestation or resorbed their embryos completely Litters of 29 females whose pregnancy was interrupted after the thirteenth day were examined One litter was removed on the thirteenth day (8 fetuses), 2 on the fourteenth day (16 fetuses), 7 on the fifteenth day (54 fetuses), 11 on

¹⁰ Hubbell, R. B., Mendel, L. B., and Wakeman, A. J. *J. Nutrition* **14**: 273, 1937

the sixteenth day (68 fetuses), 5 on the seventeenth day (14 fetuses), 1 on the eighteenth day (7 fetuses), 1 on the nineteenth day (9 fetuses) and 1 on the twentieth day (2 fetuses) Seven mothers carried their young to term Thirty-nine mature young were obtained from them Twenty-one of these were born alive, and 18 were stillborn



Fig 1—Abnormal “open eye” in a newborn rat

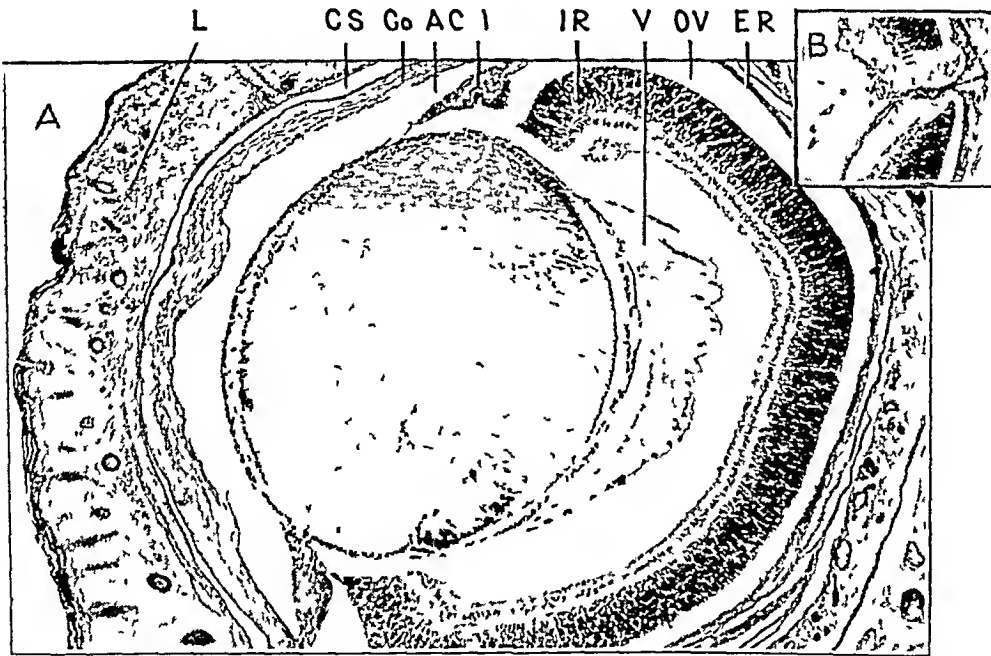


Fig 2—*A*, section of the eye of a normal newborn rat (approximately $\times 33$) In this figure, and in figure 4, *L* indicates lower lid, *CS*, conjunctival space, *Co*, cornea, *AC*, anterior chamber, *I*, iris, *IR*, internal leaf of retina, *V*, vitreous, *OV*, space of optic vesicle, *ER*, external leaf of retina

B, region of the optic nerve of the same eye (approximately $\times 33$)

Twenty-five of the young born at term showed an external abnormality of the eye In place of the closed eye of the normal newborn

rat "open eyes" (fig 1) were seen. This open eye, which showed sometimes a red discoloration between the rudimentary lids, was present bilaterally in 22 young and unilaterally in 3 young. Serial sections were made of the heads of 16 of these young. Some of them had open eyes, and in others the eyes appeared externally normal. However, all the eyes sectioned proved abnormal on histologic examination. The degree of abnormality varied, but a fibrous retrolenticular membrane containing the vascular network of the hyaloid artery was seen in all the eyes examined.

The long axis of the eye of the newborn rat deviates from the sagittal plane, since its anterior end points anterolaterally. In spite of this deviation, in the following description the region of the anterior pole of the eyeball will be called "anterior" and that of the posterior pole "posterior," although "anterolateral" and "posteromedial" would be more correct. The sections were made in the frontal plane, proceeding in a ventrodorsal direction from the nostrils to the pharynx.

Three representative sections of an abnormal eye will be described in the following paragraphs.

Figure 3 illustrates a ventral section through the right eye of an abnormal newborn rat, which showed externally a definite red discoloration in the region of the eyes. Superficial comparison with figure 2A, a ventral section through the eye of a normal newborn rat, discloses a number of defects in the abnormal eye. In the anterior portion is found almost complete obliteration of the lower conjunctival sac and of the intraocular chambers. No traces of the upper conjunctival sac can be seen. Behind the point of junction of the upper and lower lids, the sclera and the external leaf of the retina are recognizable. The space between the lower conjunctival sac and the lens is occupied by a dense tissue, which apparently represents the mesoderm, which in the normal eye contributes to the formation of the cornea and of the iris. The lens appears essentially normal. The margin of the optic cup extends forward well past the equator above and barely reaches the equator below, so that the lower parts of the lens are in direct contact with mesodermal tissue. This defect in the lower portion of the cup represents the anterior portion of the persisting fetal fissure. The vitreous is not developed. The internal leaf of the retina is approximately of normal thickness but of completely abnormal structure. This will be described in detail later. The external leaf of the retina consists of a single layer of epithelial cells. The space between the two layers, the lumen of the optic vesicle, is filled with blood. The upper margin of the optic cup, which is placed in front of the equator of the lens, is formed by the junction of the outer and the inner leaf of the retina. The internal leaf decreases abruptly in height near the margin. The

angle between the external and the internal leaf is wide open, and its sides represent the rudiments of an iris

In figure 4, which is a section approximately through the center of the eye, the lids appear to be closed, and a line of fusion is visible. This line of fusion traverses the lids in an oblique direction, and its cells are directly connected with those that fill out the conjunctival sac. The conjunctival space is not developed, since the palpebral and the

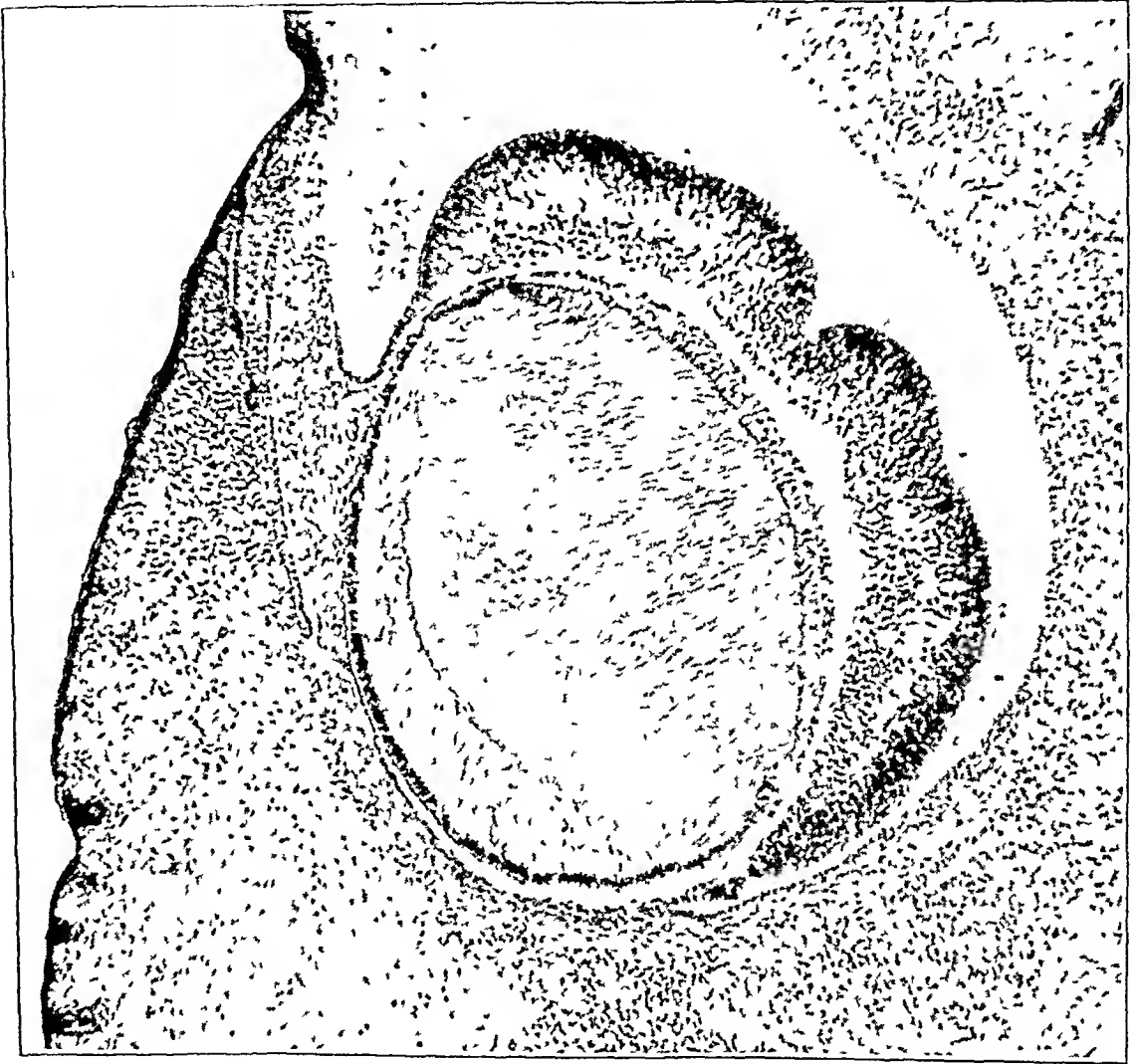


FIG 3—Section of the eye of an abnormal newborn rat, showing the lack of differentiation in the anterior parts of the eye (approximately $\times 80$). The lower part of the optic cup does not enclose the lens.

bulbar conjunctival epithelium are in close contact. The bulbar epithelium adheres firmly to a mass of mesodermal tissue, which corresponds to the cornea and probably also to the stroma of the iris. This mesodermal tissue can be divided into a loosely woven anterior part and a dense posterior part. The dense portion is covered posteriorly by a complete row of epithelial cells, which is a direct continuation of

the external leaf of the retina. Thus, the anterior chamber, the iris, the ciliary body and the posterior chamber cannot be recognized as individual structures. Behind the epithelial cells of the external leaf a linear space is seen, which represents a part of the cavity of the optic vesicle. This space enlarges toward the upper part of the eye, where it becomes dome shaped. It forms only a narrow cleft in the lower

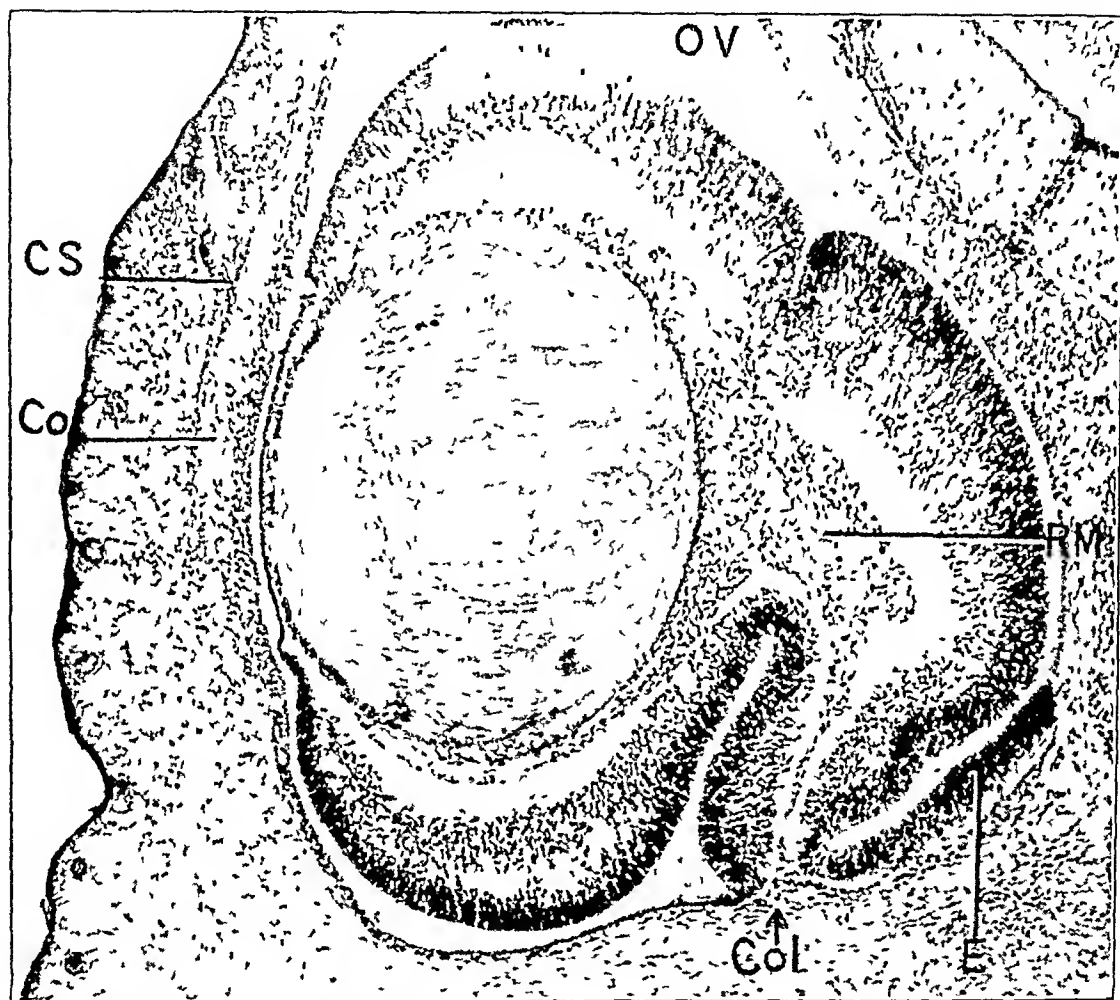


Fig 4—Section of the eye of an abnormal newborn rat, showing coloboma (*Col*), eversion of the retina (*E*) and fibrous retrolenticular membrane (*RM*) connected with extraocular mesoderm (approximately $\times 80$)

and posterior portion of the eye. The internal leaf of the retina is of approximately normal thickness with the exception of the most anterior part, which forms a single layer in front of the lens. This layer corresponds to the pigment layer of the normal iris (pars iridica retinae). The lower and posterior part of the internal leaf of the retina is split by a strand of connective tissue which connects extraocular meso-

derm and the retrolenticular connective tissue replacing the vitreous humor. This fibrous tissue, which occupies the space of the vitreous, consists of a dense network of cells in which a number of capillaries can be discerned. The connective tissue cells immediately behind the lens have small, dark and oblong nuclei, the long axes of which run parallel with the posterior surface of the lens. The network of cells between the capillaries is somewhat looser, and larger, round nuclei which are poor in chromatin are interspersed with dark, small nuclei. There is no sharp borderline toward the layer of nerve fibers of the retina. The fibrous retrolenticular tissue decreases in thickness toward the equator of the lens, where it ends. The apparent split of the retina by mesodermal tissue represents an oblique section through the fetal fissure somewhat behind the equator of the eye. The internal leaf of the retina forms several folds and is distinctly everted behind the point where the retrolenticular and the extraocular mesoderm join. Thus, there is a duplication of the internal leaf of the retina, and the "innermost" layers of the everted portion are turned outward and face the choroidea. Posteriorly the everted retina ends abruptly, it diminishes in height at the point of junction with the external leaf of the retina, which consists of a single layer of cells. In the areas not folded the internal leaf of the retina is of normal thickness, it has differentiated into two ill defined layers of cells, separated by a loose network of fibrils. The denser outer layer consists of twelve to fifteen rows of cells with round, light nuclei. Within the loose cellular layer, a layer of nerve fibers can be seen.

Figure 5 represents a dorsal section through the right eye of another abnormal newborn rat near the optic nerve. The internal leaf of the retina is folded in many places and everted below and anterior to the retinal cleft. The center of the cleft is traversed by a thick strand of connective tissue which links extraocular mesoderm with the retrolenticular fibrous membrane. This strand is pierced in its entire length by a long and thin blood vessel, which is lined by a single layer of endothelial cells. In the retinal gap nerve fibers are seen on both sides of the mesodermal strand. In more dorsal sections this strand becomes thinner and more enclosed in nerve fibers.

The sections described illustrate some of the more obvious anomalies seen in the eyes of the young of mothers fed a diet deficient in vitamin A. In spite of variations in the individual eyes, certain features common to the majority of them can be discussed. The abnormalities of the lids vary greatly. Externally they may appear closed, although the line of fusion is abnormal. Their conjunctival surface is frequently closely attached to the corneal epithelium, since the conjunctival space does not develop. In "open eyes" the lids are not fused, and an

abnormal, fibrotic and often blood-tinged tissue is found in place of the cornea within the palpebral fissure. In case of absence of the anterior chamber a thick mesodermal membrane is seen between the lids, on one side, and the external leaf of the retina or the lens, on the other side. This membrane consists of the two layers of different texture. The anterior layer appears to correspond to the substantia propria of the cornea, and the denser posterior layer, to the stroma of the iris. The iris is present in a rudimentary form only. Its stroma



Fig 5—Section of the eye of an abnormal newborn rat near the optic nerve, showing coloboma, eversion of the retina and a fibrous band which links the retrolenticular membrane with extraocular mesoderm (approximately $\times 66$)

is in the central ("pupillary") area closely connected with the anterior pole of the lens. In its peripheral parts it is covered posteriorly by the external leaf of the retina. The most anterior part of the internal leaf of the retina, which consists of a single layer of cells (fig 3) and which corresponds to the pigment layer of the mature iris, is separated throughout from the external leaf by the lumen of the optic vesicle. Thus many features of the fetal rudiments of the iris are maintained in these abnormal eyes of young born at term.

Extensive changes are found in the lower parts of the optic cup. These areas, which are phylogenetically and ontogenetically the youngest parts of the eye, are particularly susceptible to modification and mutation¹¹. The first section described (fig 3) shows the optic cup open anteriorly in its lower part. While the cup encloses completely the upper half of the lens, the failure of the fetal fissure to fuse in this region makes it appear as though the lower half is not encased in the ectodermal parts of the eye but rests directly on mesoderm. The second

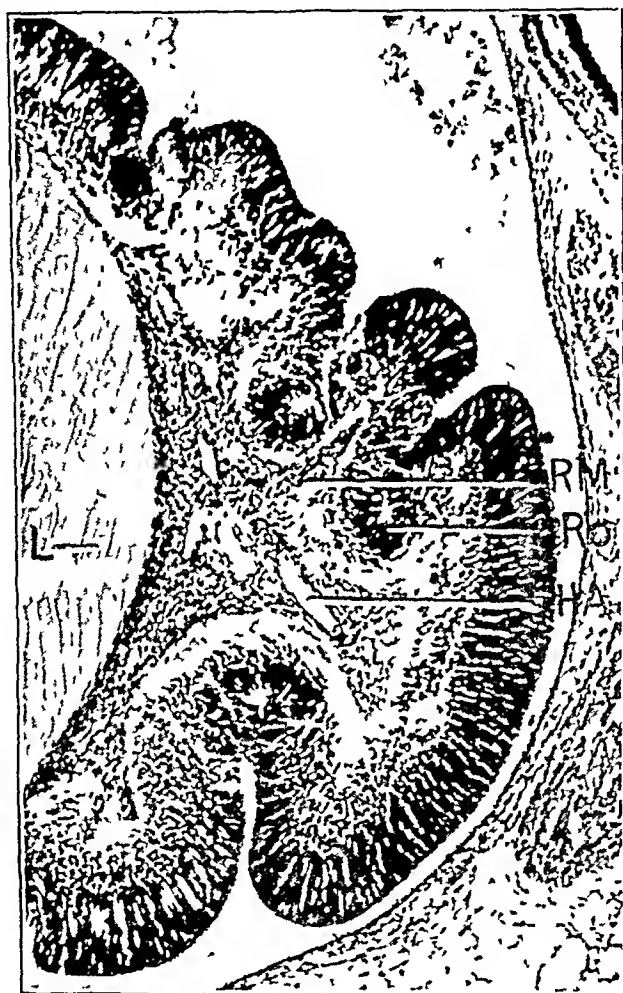


Fig 6—Section through posterior portion of an abnormal eye. *L* indicates the lens, *RM*, the retroreticular membrane, *Ro*, rosette, *HA*, branch of hyaloid artery (approximately $\times 70$)

section (fig 4) illustrates a gap in the lower part of the optic cup and eversion of the retina posterior to it. The gap is traversed by a strand of mesodermal tissue. The third section (fig 5) shows also a retinal cleft with retinal eversion near the optic nerve. Within the fibers of the optic nerve a thick band of mesodermal tissue is seen, which

¹¹ Mann, I. C. *Developmental Abnormalities of the Eye*, Cambridge, England, Cambridge University Press, 1937

encloses remnants of the hyaloid artery. This mesoderm spreads out behind the lens and occupies the space taken by the corpus vitreum in the normal eye. The mesodermal band, as well as the mesodermal retrolenticular membrane (figs 4 and 5) seen in these sections, is definitely overgrown, as compared with the retrolenticular tissue in

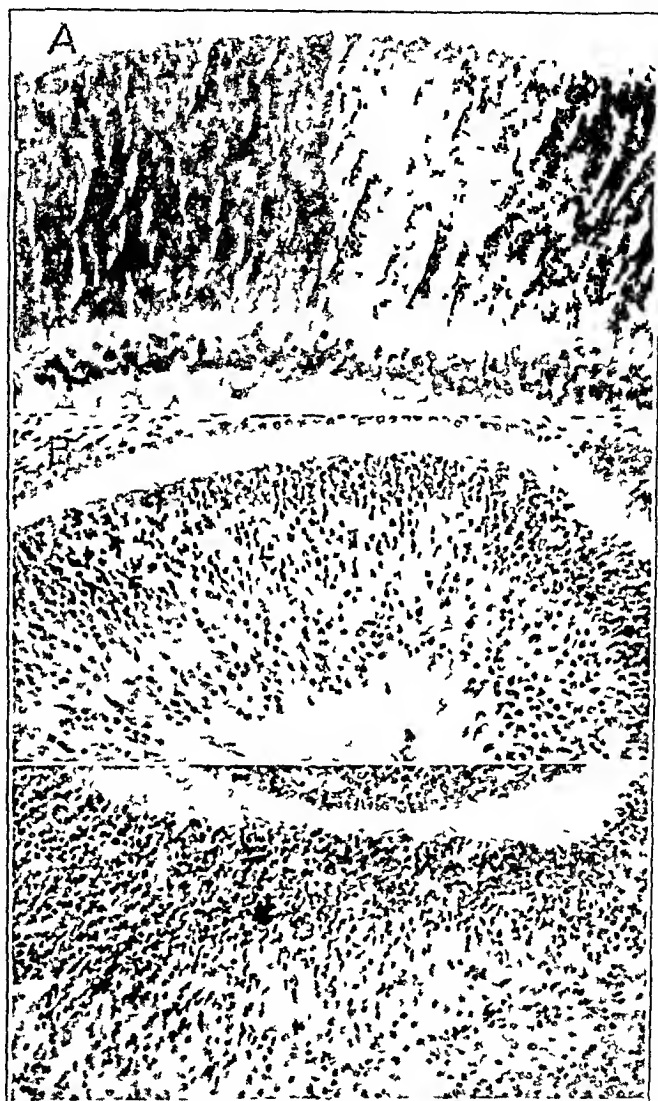


Fig 7—Sections of (A) retina of normal newborn rat, (B) retina of abnormal newborn rat enclosing space of the optic vesicle, (C) brain tissue of abnormal newborn rat, enclosing parts of lateral ventricle (approximately $\times 160$)

normal fetuses. The changes in the lower parts of the optic cup—persistent fetal fissure, eversion of the retina and penetration of the cup by mesodermal tissue—are characteristic of the typical coloboma. In some abnormal eyes the posterior portions of the internal retinal leaf form many folds (figs 5 and 6). These folds when cut transversely appear in the sections as “isettes,” in which the retinal cells are radially

arranged around a well defined inner circle. The space within this circle corresponds to the cavity of the fold, which is a part of the lumen of the optic vesicle. The histologic structure of the internal leaf of the retina shows little resemblance to that of the retina of a normal newborn rat. This is well borne out by a comparison of *A* and *B* of figure 7, in fact, the abnormal retina (fig 7*B*) resembles brain tissue (fig 7*C*) rather than normal retinal tissue. Hemorrhages are frequently seen in the abnormal eyes. They can be found in the orbits, in the cavity of the optic vesicle, in the retina and near the palpebral fissure.

In our opinion, the sections just discussed are representative of the congenital malformations of the eye found in the young of vitamin A-depleted rats. However, there were variations in the eyes of the 16 abnormal young that were examined histologically. As mentioned, the serial sections of all 32 eyes showed a fibrous retrolenticular membrane. In both eyes of 1 animal this membrane was apparently the only abnormality present. This rat was the only member of the litter that was carried to term. If there had been other fetuses in this litter, they were resorbed in the early stages of development. In 10 eyes the retrolenticular membrane was continuous with a thick strand of connective tissue which was embedded in the optic nerve and was carried along with it into the eye, but there were no signs of coloboma. In 13 eyes there were similar retrolenticular tissue and a retinal gap and eversion near the optic nerve, that is, coloboma of the disk. In 1 eye such a coloboma combined with a peripheral or anterior coloboma, but the two fissures were not continuous. Four eyes had complete colobomas, which were continuous from the region of the disk to the anterior part of the eye. In 30 eyes the structure of the retina was abnormal (fig 7). In 28 eyes the iris and the ciliary body were rudimentary or abnormal, and in 28 eyes the anterior and posterior chambers were not formed. The mesoderm, which corresponds to the stroma of the cornea and of the iris, was partly or completely fused anteriorly with the conjunctival epithelium in 18 eyes and was fused posteriorly with the epithelium of the external retinal leaf in 30 eyes. The conjunctival sac was partly or completely occluded in 18 eyes. Seventeen of the 32 eyes sectioned were "open" and 15 closed. As a rule the character and degree of abnormalities were similar in litter mates. However, there were exceptions to this rule, and variations in the eyes of litter mates, as well as in the eyes of one and the same animal were seen.

Most of the young with abnormalities of the eyes also had malformations of other soft tissues and of the skeleton. The changes observed in the other organs will be described in another communication. Although removed at term, the average weight of the young was only 3.4 Gm.

The following control experiments were undertaken. Eighty-six mothers of the Sprague-Dawley strain fed an adequate stock diet had

1,183 young which on careful inspection did not show "open eyes" at birth. Serial sections were made of the eyes of 20 of these young. None of the abnormalities just described were found in the 40 eyes examined. Sixty-four females of the same strain were raised on an adequate diet and bred on the purified diet W supplemented with 60 U S P units of vitamin A daily. They had 423 young, none of which had open eyes at birth. Ten females were raised on the preparatory diet U and bred on the purified diet W supplemented with 60 U S P units of vitamin A daily. They had 103 young, none of which were born with open eyes. The eyes of 18 of these young were

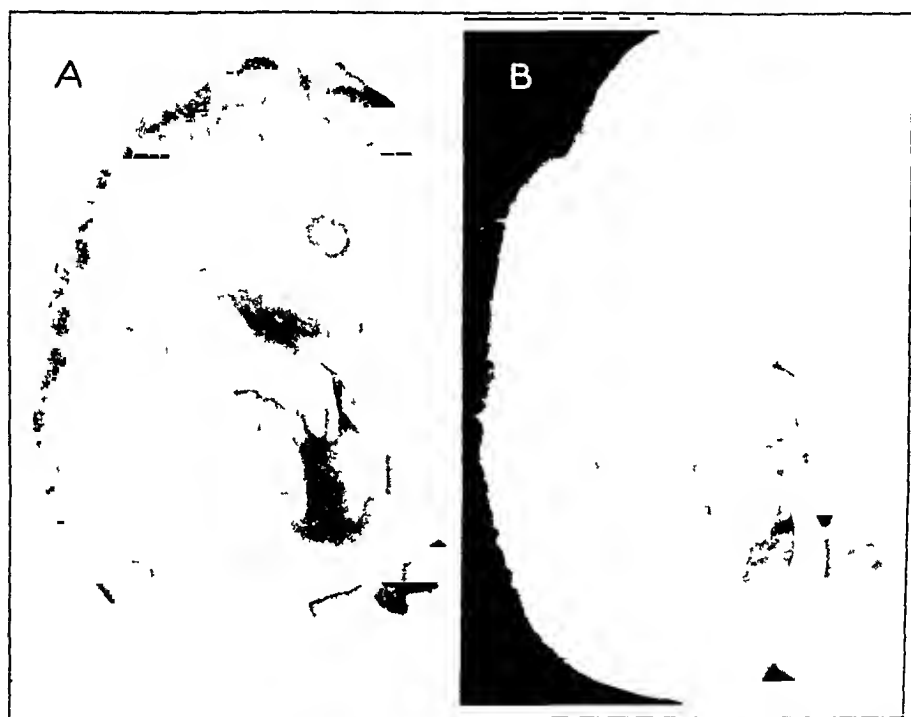


Fig 8—*A*, normal rat fetus approximately 16 days old, *B*, abnormal rat fetus approximately 16½ days old. The eye is not seen externally.

sectioned serially and all 36 eyes were examined and found normal. Twelve females were raised on diet U and bred on diet W without giving birth to young. After they had lost about 40 Gm of weight and had begun to show pronounced signs of vitamin A deficiency, they were given large amounts of vitamin A until they recovered and sexual cycles were restored. Then they were bred again and 54 young were obtained. None of these had open eyes. The eyes of 4 of these young were serially sectioned, and all 8 were found normal. Thus the abnormalities of the eyes described were found only in the young of mothers raised on diet U and bred on diet W. Female rats fed an adequate diet or diet W supplemented with vitamin A during pregnancy had young with normal eyes.¹²

(Footnote on next page)

EMBRYOLOGIC STUDIES

One hundred and fifty-four fetuses were removed between the fifteenth and the twentieth day of gestation from mothers reared on diet U and bred on diet W. The majority of these females were killed because they showed signs of beginning resorption. Many 15, 16 and 17 day old fetuses of this origin could be recognized externally as abnormal. The eyes of normal fetuses 15 to 17 days old have open palpebral fissures, since the lids do not develop and fuse before the eighteenth day of prenatal life. In most of the abnormal fetuses 15 to 17 days old the palpebral fissures could not be seen, and the eyes appeared absent or deeply embedded and removed from the surface (fig 8 B).

Figure 9 illustrates the development of the normal eye from the fifteenth to the eighteenth day of prenatal life (*A*, *B*, *C* and *D*), as compared with the development of the abnormal eye (*E*, *F*, *G* and *H*). On the fifteenth day the normal eye (fig 9 *A*) has an open palpebral fissure and is enclosed in a semicircular elevation which protrudes from between the rudimentary eyelids. The cornea lies on the surface of the body. It is a thin membrane, which consists of surface epithelium and one layer of mesodermal cells. The iris and ciliary body are not yet developed. The fetal fissure has closed. Between the lens and the retina a loose network of cells is seen, which consists of capillaries of the hyaloid system. The optic nerve is slightly closer to the lower than to the upper margin of the optic cup. Above the optic nerve the external leaf of the retina is somewhat thickened but well demarcated from the internal leaf. In the abnormal eye of a fetus of the same age (fig 9 *E*) the lens is separated from the surface epithelium by mesodermal tissue which is much thicker than the normal cornea. The lens and the optic cup therefore appear far removed from the surface of the body. The cup is wide open near the optic nerve, since the retina is everted below the nerve. Through the opening enter, in addition to the optic nerve, the hyaloid artery and a band of mesodermal connective tissue which links extraocular mesoderm with the dense fibrous retrolenticular tissue. The everted parts of the retina decrease gradually in height. The coloboma illustrated in figure 9 *E* can be traced through anterior sections, which show that in this eye the fetal fissure is open its entire length.

In the section of the eye of a normal 16 day old embryo (fig 9 *B*) it can be seen that the cornea has increased in thickness. The mesodermal tissue consists of several layers of cells and is posteriorly limited by an endothelium. A pupillary membrane divides the space

12 "Open eyes" were found in 3 of 2,000 young born of female rats of the Sprague-Dawley strain that had been bred on a diet deficient in riboflavin (Warkany, J, and Nelson, R C. *Anat Rec* 79: 83, 1941. Warkany, J, and Schraffenberger, E J. *Nutrition* 27: 477, 1944). These eyes were serially sectioned and showed no retrolenticular membrane and no coloboma. The iris and the retina were normal.

posterior to the cornea into two compartments. The optic nerve divides the cup into two equal parts. The lumen of the hyaloid artery can be seen in the center of the nerve stem. The layer of nerve fibers is developing in the internal leaf of the retina, and formation of the vitreous



Fig 9 A-D —Sections of (A) eye of normal rat fetus approximately 15 days old, (B) eye of normal rat fetus approximately 16 days old, (C) eye of normal rat fetus approximately 17 days old, and (D) eye of normal rat fetus approximately 18 days old (A and B approximately $\times 80$, C and D approximately $\times 62$)

in the retrolenticular space has taken place. Few capillaries of the hyaloid system can be seen in this space. The abnormal eye (fig 9 *F*) is separated from the surface by a thick layer of mesodermal tissue, which

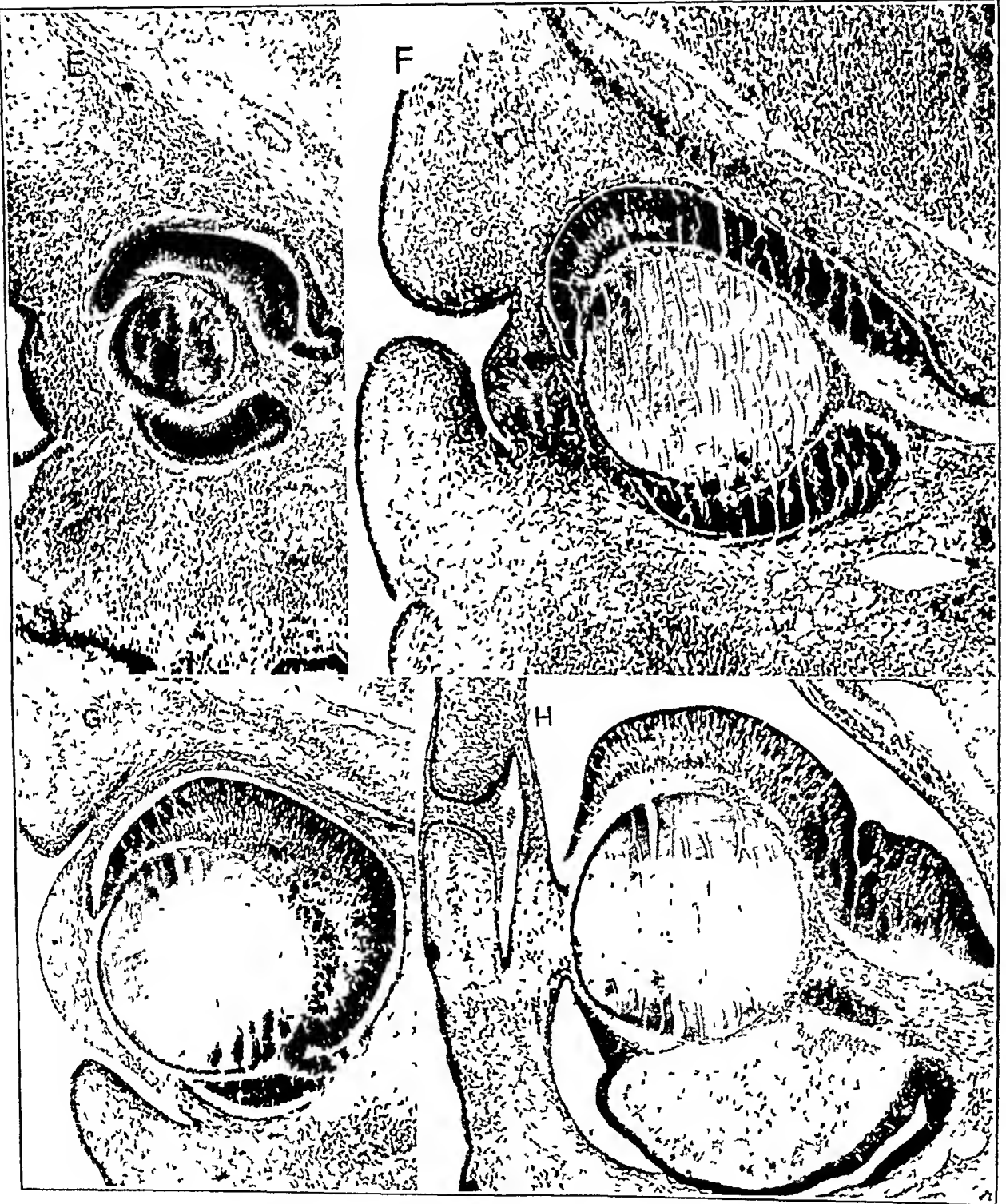


Fig 9 *E-H*—Sections of (*E*) eye of abnormal rat fetus approximately 15 days old, (*F*) eye of abnormal rat fetus approximately 16 days old, (*G*) eye of abnormal rat fetus approximately 17 days old and (*H*) eye of abnormal rat fetus approximately 18 days old (*E* and *F* approximately $\times 80$, *G* and *H* approximately $\times 62$)

is covered by surface epithelium. In front of the region of the eye two folds of skin are formed, which almost meet. The mesodermal tissue in front of the eye is in close contact with the anterior epithelium of the lens, so that the space usually present in the normal eye anterior to the lens appears entirely occluded. The optic nerve divides the optic cup into two unequal halves. The upper half is much longer and reaches farther forward than the lower half. Such proportions are seen in earlier embryonic stages of normal eyes but not in the normal 16 day old fetus. At this age they indicate an arrest of development.

Figure 9 C represents the eye of a normal 17 day old fetus, the section reproduced is ventral to the entrance of the optic nerve. The lids are still open. The chamber is well developed, but the iris is still absent. The vitreous is clearly seen. The internal leaf of the retina shows no formation of layers, but it is lined toward the vitreous by a stratum of nerve fibers. Figure 9 G illustrates the appearance of the eye of an abnormal 17 day old fetus. The anterior parts of this eye are normal, the lids are open, the cornea is of normal thickness, and a narrow chamber is seen. In contrast to the normal eye, there is a loose arrangement of the cells of the internal retinal leaf. The vitreous is absent, and its place is taken by a thin layer of connective tissue cells, this layer of retrolenticular fibrous tissue is much better developed in dorsal sections of the same eye. A cleft of the retina with eversion of the internal retinal leaf is seen in the lower part of the optic cup. This cleft represents a coloboma, which in this case extends throughout the length of the eye.

The eye of the normal 18 day old fetus (fig 9 D) is covered by eyelids which are completely fused. A wide conjunctival space has formed, the cornea and the anterior chamber are well developed, and a primitive iris can be recognized. It consists of two layers, the distal one being a continuation of the external retinal leaf which is covered toward the anterior chamber by cells of mesodermal origin. The posterior layer of the iris is the most anterior part of the internal retinal leaf. Between the two leaves the space of the optic vesicle can still be recognized. Between the margins of the cup the pupillary membrane is seen. The space of the vitreous has increased in size. In the internal leaf of the retina three layers can be distinguished: a dense outer nuclear layer, an inner nuclear layer of lesser density and the layer of nerve fibers. The blood vessel embedded in the optic nerve divides into numerous capillaries as soon as it reaches the vitreous.

The eye (fig 9 H) of an abnormal 18 day old fetus is covered by lids which are completely fused. The conjunctival space exists in rudimentary form only. A thick layer of mesodermal tissue takes the place

of the cornea and of the anterior chamber. The margin of the optic cup represents the rudiments of the ectodermal parts of the iris. There is no vitreous, but a retrolenticular fibrous membrane is seen in its place. This membrane is linked with extraocular mesoderm by a band of connective tissue. There is a coloboma of the retina. The layers of the upper parts of the internal leaf of the retina are not well defined, and the structure of its lower parts has been destroyed by a hemorrhage. Blood cells can be seen below the lens and below the fibrous retrolenticular tissue.

The abnormal eyes of fetuses 19 to 21 days old resemble the eyes of mature abnormal young so much that it seems unnecessary to describe them here.

COMMENT

The experiments described in this report were planned as a study of the effects of extreme maternal vitamin A deficiency on the fetus. To this end the female rats of the parent generation were raised on a preparatory diet (diet U) which contained enough carotene to make possible growth and maturation but prohibited storage of vitamin A. At maturity the rats were placed on a purified diet (diet W) which was completely free of carotene and vitamin A. While on this diet the females were bred to normal males of the same strain. The mothers showed signs of vitamin A deficiency within one or two weeks, and their young presented, among other malformations, the ocular defects described. This method appears to induce a borderline deficiency in the mothers which in some instances permits termination of pregnancy at term, although the development of the young suffers. In other instances the females do not breed, or they resorb their young.

As controls, females of the same strain were raised and bred on an adequate diet. No congenital defects of the type described in this communication were found in the offspring. They were also absent in the offspring of females raised on the preparatory diet U and bred on diet W when the latter was supplemented with vitamin A. This permits the conclusion that vitamin A in the maternal diet prevents the defects in the young.

These congenital abnormalities of the eyes consist partly of structures arrested in early ontogenetic stages and partly of formations that do not correspond to normal embryonic conditions. The coloboma and eversion of the retina, its penetration by mesodermal tissue, the low insertion of the optic stalk in the cup, the absence of the chambers and the lack of fusion of the constituents of the iris can be explained by arrest of development. However, the overgrowth of connective tissue between the hyaloid vessels in the place of the vitreous and the peculiar structure of the retina have no equivalents in early fetal stages.

Some of the ocular malformations induced by maternal vitamin A deficiency resemble those seen in the defective eyes which are hereditary in certain strains of rabbits. These eyes, which have been thoroughly studied by von Hippel,¹³ von Szily,¹⁴ Koyanagi¹⁵ and others, show coloboma, eversion of the retina and often microphthalmos and orbital cysts. However, the mesodermal tissue which enters the fetal fissure remains fine and delicate and is not always present. In the abnormal eyes described in this communication the corresponding mesodermal tissue is firm and closely knitted, it could be demonstrated in all abnormal eyes which were histologically examined. Orbital cysts and microphthalmos were not observed. These differences are of considerable theoretic interest, since the theories of causation of colobomas have been decidedly influenced by the changes observed in the eyes of rabbits of colobomatous stock.

The fact that a malformation such as coloboma, which has been observed as a hereditary defect, can also be induced by maternal dietary deficiency is in agreement with the conception¹⁶ that a specific malformation can be the result of a genic mutation in 1 case and of an environmental modification in another. The coloboma induced by maternal nutritional deficiency represents a "phenocopy"¹⁷ of the colobomas which are genetically determined.

In the description of the abnormal eyes we have emphasized certain anatomic features and have disregarded others which require further investigation. There is also need for additional experimental work which will aid in the explanation of the mechanism by which the defects are brought about. It is planned to ascertain the critical period in which the abnormalities are determined by supplementing the deficient diet with vitamin A on the various days of gestation, and experiments are in progress on the fate of some of the abnormal structures in post-natal life.

SUMMARY

When female rats were raised and bred on a dietary regimen which led to extreme vitamin A deficiency during pregnancy, congenitally deformed offspring were obtained. These newborn rats had various

13 von Hippel, E. *Arch f Ophth* **55** 507, 1903

14 von Szily, A. *Ztschr f d ges Anat (Abt 1)* **84** 1, 1924

15 Koyanagi, Y. *Arch f Ophth* **104** 1, 1931

16 Landauer, W. *Arch f Entwcklungsmechn d Organ* **110** 195, 1927. Dunn, L. C., in *Harvey Lectures, 1939-1940*, Lancaster, Pa., Science Press, 1940, pp 135-165. Warkany, J., Nelson, R. C., and Schraffenberger, E. Congenital Malformation Induced in Rats by Maternal Nutritional Deficiency. IV. Cleft Palate, *Am J Dis Child* **65** 882 (June) 1943.

17 Goldschmidt, R. B. *Physiological Genetics*, New York, McGraw-Hill Book Company, 1938.

defects of the skeleton and of some of the soft tissues. Histologic sections of the eyes were studied, and a fibrous retrolenticular membrane was found in place of the vitreous in every specimen. In addition, there were frequently colobomas, eversion and abnormal structure of the retina, rudimentary development of the iris and of the ocular chambers, defects of the cornea and of the conjunctival sac and lack of fusion of the lids. In case of the last defect the abnormal eyes could be recognized by external inspection. When the maternal diet was supplemented with vitamin A during pregnancy, the eyes of the young were normal.

CORNEAL TRANSPLANTATION AND PRELIMINARY IRIDECTOMY

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THE technic of corneal transplantation is a well established procedure Iridectomy as a preliminary operation is here offered and recommended, for the following reasons

(1) It enables the surgeon to estimate the amount of postoperative reaction that may follow in the eye concerned, (2) it allows for more rapid formation of the anterior chamber, (3) there is less likely to be a prolapse of the iris into the wound after the transplantation

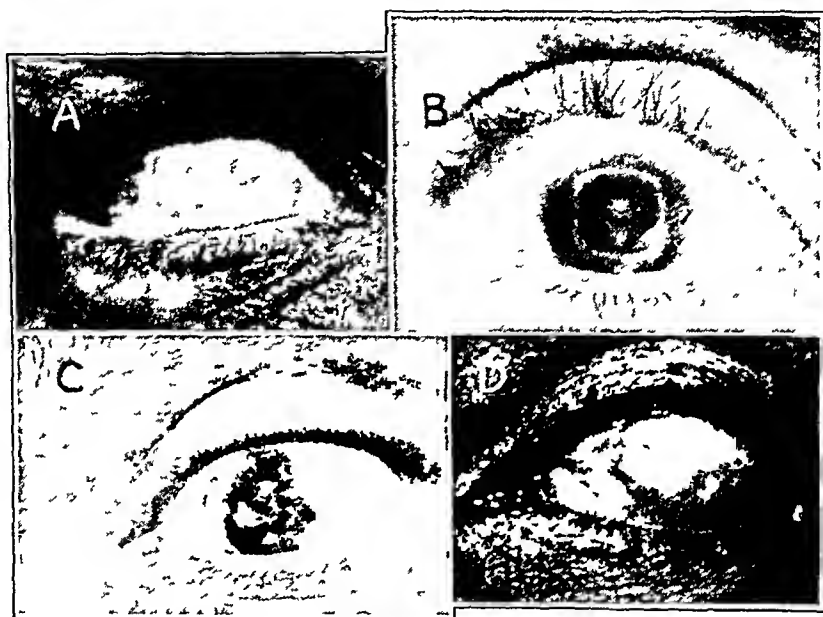
A preliminary iridectomy will enable the surgeon to study the eye involved under operative conditions This does not apply so rigidly in cases in which an avascular nebulous cornea is present, such as may follow extensive phlyctenular keratitis or a central leukoma resulting from ulcer But in cases of old interstitial keratitis resulting from syphilis or tuberculosis, in which infiltration is deep and the vascularity potentially marked, it is of value to determine the reaction that may result from a simple iridectomy before one does a major operation, such as a corneal transplantation Severe keratitis has been observed to result from iridectomy in a case of the latter procedure If the vascularity becomes marked, either a peritomy or cauterization of some of the larger vessels can be carried out to great advantage

The reactivation of a previous underlying inflammatory process can result in an increase in intraocular tension, for in many cases of old interstitial keratitis there has been associated iritis or uveitis In one of my cases low grade keratitis followed the iridectomy, and after this had subsided a rise in intraocular tension occurred (figure A) This was remedied by a filtering operation, before the eye was ready for corneal transplantation It is better to deal with such complications before the final operation as the graft will then have more favorable circumstances under which to adhere and remain transparent

The development of glaucoma as a complication following corneal transplantation must be constantly kept in mind, and the surgeon should do everything in his power to avert this difficulty The occur-

From the Department of Surgery Division of Ophthalmology, Western Reserve University School of Medicine

rence of this complication is frequently mentioned in case reports. Rapid reformation of the anterior chamber is essential to prevent adhesions at the chamber angle that may subsequently cause a rise in intraocular tension. If the graft and cornea of the recipient have been properly cut and the fit is as tight as it should be, the preliminary iridectomy will offer ideal conditions for a rapid reformation of the chamber. In all the 25 cases in which I carried out this procedure the anterior chamber was of normal depth within the first twenty-four hours. In 3 of these cases a second operation was performed because the graft had become opaque, and in none of them was there an increase in intraocular tension, all chambers reforming rapidly.



A, tuberculous interstitial keratitis, *B*, sclerectomy for glaucoma following a transplantation for keratoconus, *C*, hazy graft and prolapsed iris showing iridectomy, *D*, interstitial keratitis.

Two striking examples of the need of preliminary iridectomy to prevent glaucoma have been brought to my attention. After a transplantation for keratoconus, in the case illustrated in *B* there developed an increase in intraocular tension reaching 50 mm. of mercury (Schiotz), with redness and edema of the cornea. A LaGrange sclerectomy was performed, and with miotics the tension was restored to normal and has remained so since, a period of one year. *C* of the figure illustrates a similar case. In this case an increase in intraocular tension developed after corneal transplantation. The iris became incarcerated on one edge of the wound, as can be seen in the illustration. The graft at no time was of normal transparency. After operation the intraocular tension gradually became elevated, and two months after the original operation an iridectomy was necessary. This controlled the

pressure. However, the graft must be done again if this patient is to benefit from a corneal transplant.

Experimentally, the clinical evidence for rapid reformation of the anterior chamber as related to iridectomy is not substantiated, for in the animals used (rabbits) the aqueous has an extremely rapid flow on opening the chamber and consequently the chamber is restored almost immediately.

A prolapse of the iris into the corneal wound is less likely to occur if preliminary iridectomy has been done. This is especially true if the anterior chamber has failed to resume its normal depth within a reasonable period. Also, if a cataract extraction is to follow the transplantation, the displacement forward of the vitreous which may follow removal of the lens may dangerously narrow the distance between the iris and the cornea, predisposing to postoperative glaucoma.

If relatively clear cornea is present near the periphery and the surgeon decides to place the graft away from the center of the cornea, near one limbal region, preliminary iridectomy in this spot will be especially valuable, as a prolapse of the iris would otherwise easily follow.

There is one group of cases in which an iridectomy may prove dangerous and may complicate the operative procedure that is to follow. It should be approached with caution in an eye which shows the relatively unfavorable deeply scarred, somewhat vascular cornea and in which when the anterior chamber is opened the iris is found to be smooth and bound down tightly to the lens or to its remnants. Loss of vitreous easily follows an iridectomy in such an eye, for the vitreous is often fluid as the result of the previous inflammatory process. If this condition exists, the wound should be sutured without iridectomy and the transplantation attempted later. *D* of the figure illustrates this type of eye.

The opinion has been voiced that preliminary iridectomy is unnecessary in such cases and merely subjects the eye to another surgical procedure. However, iridectomy is in itself a relatively simple operation and should not be feared if it will be a safeguard and help in performing a major operation later. *B* and *C* of the figure illustrate what can be avoided by carrying out this procedure.

SUMMARY

Iridectomy as a preliminary operation to corneal transplantation is recommended for the following reasons: (1) It enables the surgeon to evaluate how an eye will withstand surgical procedure, (2) the risk of glaucoma can be greatly lessened, (3) the possibility of prolapse of the iris is made unlikely.

CONTACT EYE CUP FOR CORNEAL BATHS WITH SOLUTIONS OF PENICILLIN

LIEUTENANT COLONEL GILBERT C STRUBLE
AND
MAJOR JOHN G BELLOWS
MEDICAL CORPS, ARMY OF THE UNITED STATES

THE value of local applications of solutions of penicillin in the treatment of certain inflammatory diseases of the eye is now generally recognized. Experimental and clinical evidence has shown this to be particularly true in cases of diseases of the anterior segment of the globe.¹ Experimentally, in cases of this type relatively high concentrations of penicillin in the cornea, conjunctiva, sclera, aqueous, iris and ciliary body and small amounts in the vitreous can be built up by use of the corneal bath and by subconjunctival injection.² High degrees of penetration of penicillin have also been attained with iontophoresis.³

It has been our experience that administration of penicillin as eye drops by simple instillation will effect the prompt cure of the acute inflammatory diseases of the conjunctiva caused by penicillin-sensitive organisms.² In the treatment of corneal ulcers, however, particularly in cases in which the deeper layers of the cornea are involved, the instillation of penicillin locally as eye drops, even though done every hour, has proved inadequate. This is due to the rapid loss of the penicillin through the lacrimal apparatus, to rapid dilution with the tears and to diffusion.

The corneal bath is a simple method of producing a high content of the drug in the tissues of the anterior segment of the globe.² Such concentrations are desirable in cases of deep corneal infection, such as serpent ulcer. The ordinary commercial eye cup is found to be unsatisfactory for the following reasons:

From the Department of Ophthalmology, Billings General Hospital, Fort Benjamin Harrison, Ind.

1 Robson, J. M., and Scott, G. I. Local Chemotherapy in Experimental Lesions of the Eye, *Lancet* **1** 100, 1943. von Sallmann, L. Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infection with *Pneumococcus*. *Arch. Ophth.* **30** 426 (Oct.) 1943, Penicillin and Sulfadiazine in the Treatment of Experimental Intraocular Infections with *Staphylococcus Aureus* and *Clostridium Welchii*. *ibid.* **31** 54 (Jan.) 1944.

2 Struble, G. C., and Bellows, J. G. Studies on the Distribution of Penicillin in the Eye and Its Clinical Application, *J. A. M. A.* **125** 685 (July 8) 1944.

3 von Sallmann, L., and Meyer, K. Penetration of Penicillin into the Eye, *Arch. Ophth.* **31** 1 (Jan.) 1944.

1 An excess of penicillin solution is required to fill the cup, and a considerable amount is lost through leakage and through the lacrimal apparatus

2 The corneal lesions become contaminated from the surfaces of the skin and lashes

The patient experiences difficulty in keeping the eye open because of the pain and blepharospasm associated with the corneal ulcer

With the technical aid of Major George Powell, a suitable eye cup has been designed for corneal baths, obviously, it should prove satisfactory in the treatment of various conditions requiring corneal baths, for example, the application of miotics in cases of acute glaucoma. The contact cup is made of a clear acrylic material. It has a small knob or handle attached to its anterior curved surface to facilitate handling. Located in the upper margin are two small round openings, the larger



Above, anterior, lateral and posterior views of the contact cup, below, contact cup in place

for the instillation of the penicillin solution and the smaller for the escape of air during the process of filling the cup. This cup rests on the scleral conjunctiva under the lids, effecting an air-tight and water-tight seal. It has proved entirely satisfactory in our hands.

Cold sterilization in a solution of mercury bichloride is easily carried out. The cups should not be boiled, autoclaved or sterilized in any solution containing chloroform or ether, which are solvents of the acrylic material.

The eye to be treated is first anesthetized by the instillation of a few drops of any of the anesthetics for local use in the eye, such as tetracaine, butacaine, metycaine or phenacaine. With the patient looking down, the upper margin of the contact cup is then slipped under the upper lid, the patient is then directed to look up, so that the lower margin of the cup will drop into the lower cul-de-sac, inside the lower lid.

The cup is then filled with the prepared solution of penicillin by injecting the solution into the larger round hole, at the top of the cup. For this purpose, we have found a tuberculin syringe most suitable, using an ordinary hypodermic needle, the tip of which has been cut off and blunted. Filling is facilitated by directing the patient to look down and slightly elevating the upper lid with a finger of the left hand while injecting the fluid from the syringe with the right. During this procedure the patient may be either lying on his back or sitting erect. We prefer the latter position.

The strength of the penicillin solution used by us has varied from 1,000 to 2,500 Oxford units in 1 cc of isotonic solution of sodium chloride. We have found these dilutions to be entirely free from undesirable side effects, such as burning or smarting. The duration of the first treatment is thirty minutes, with subsequent treatments extending up to one hour. This procedure should be repeated at intervals of four to five hours in order to maintain an adequate level of penicillin in the cornea and aqueous.

The advantages of the contact bath cup are as follows:

1. Known concentrations of penicillin can be kept in contact with the anterior segment of the globe for long periods. There is no loss of fluid through the lacrimal apparatus, nor is there dilution of the solution by the tears.

2. Considerable conservation of penicillin is possible. Less than 0.5 cc of solution is required to fill the cup.

3. With adequate anesthesia the patient experiences no discomfort whatever.

4. The transparent cup permits a view of the anterior segment of the globe and the level of the penicillin solution at all times.

5. The contact cup fits either eye.

Major George Powell, director of the Dental Section of the Medical Department Enlisted Technicians School, Billings General Hospital, Fort Benjamin Harrison, Ind., gave technical assistance.

Clinical Notes

TRAUMATIC LIPORRHAGIA RETINALIS

Report of a Case

CAPTAIN OGDEN D. PINKERTON

Medical Corps, Army of the United States

TRAUMATIC liporrhagia retinalis, commonly known as Purtscher's disease, or the syndrome of the posterior pole of the eyeball, is characterized by exudation and hemorrhage in the posterior pole of a nontraumatized eye, followed (in some cases) by atrophy of the optic nerve. Precipitating factors are head injury, fractures of the vertebrae and long bones and compression injuries of the chest. In the case presented the lesion was unilateral, related to both the arterioles and the venules and terminated in almost complete atrophy of the optic nerve.

The photographs of the fundus show the advanced degree of atrophy of the optic nerve and the organized exudate in the macular area (fig *A* and *B*).

REPORT OF CASE

History—A Filipino boy aged 11 was struck and knocked to the ground by an Army vehicle on June 9, 1944. He was not rendered unconscious, but he stated that his breath was "knocked out." He was admitted to the hospital in shock, with a blood pressure of 94 systolic and 42 diastolic. Examination revealed (1) a severe lacerated wound of the left temporal and frontal areas and the left external canthus, (2) compound, comminuted, complete fracture of the anterior end of the left zygomatic bone, and (3) contusions of both sides of the face, the lower left anterior wall of the chest and the upper portion of the abdomen on both sides. The patient was mentally clear, and there was no evidence of cerebral concussion or damage.

About twenty-eight hours after admission the patient reported that he was unable to see with his right eye.

Ocular Examination—Examination six hours later revealed the following condition. Right Eye. Visual acuity was limited to perception of light peripherally, with very poor projection. There was no external evidence of injury of the eyeball, lids, conjunctiva or orbital rim. The pupil was semidilated and reacted sluggishly to light and in binocular accommodation.

Left Eye. Visual acuity was 20/20. The eyelids were ecchymotic. There were a large temporal conjunctival hemorrhage and a repaired laceration of the external canthus. The pupillary reactions were normal.

Fundus. Examination of the fundus of the nontraumatized, right, eye revealed a dense, yellowish white reflex, confined to the posterior pole. This was due to a massive yellow extravasation, which extended about 3 disk diameters superiorly, 4 disk diameters nasally, 5 disk diameters inferiorly and 4 disk diameters temporally. The arteries and veins were distinctly made out and were not covered by exudate. The exudate showed no specific relation to the arterioles or venules, being evenly dispersed between the vessels. The vessels appeared as distinct

channels on a yellowish white background. The veins were engorged. The nerve head was surrounded by exudate, but its margins were flat. There were many fresh, striated hemorrhages above and below the disk and between the disk and the macula. The hemorrhages were located along both the venules and the arterioles. The macula presented a well circumscribed, deep hemorrhage. The fundus of the traumatized eye revealed no pathologic change.

Six days later considerable peripheral absorption of the exudate had taken place. The macula presented a triangle of various colors. Centrally, it was of chocolate hue, surrounded by a ring of grayish brown, and this, in turn, was surrounded by a halo of yellow. Thirteen days after the boy's admission there was no noticeable change in the hemorrhages, but the exudate had continued to



Photographs taken three months after injury, showing organized exudate in (A) the macular area and (B) atrophy of the optic nerve head.

diminish. Thirty-one days after his admission there was complete absorption of the exudate and hemorrhage except for a small amount between the nerve head and the macula. The nerve head now presented a pronounced generalized pallor. Vision was limited to counting fingers at 3 to 4 feet (90 to 120 cm) in the temporal and superior fields only, with marked restriction of these fields.

The cholesterol content of the blood, determined three days after the patient's admission, was normal. Roentgenographic studies revealed no fractures of the orbit or the optic foramen.

Three weeks after the patient's admission to the hospital there developed atypical pneumoma of the upper lobe of the right lung and, later, of the upper lobe of the left lung, both areas cleared prior to his discharge from the hos-

pital Three months after his discharge there was a recurrence of consolidation in the upper lobe of the left lung, accompanied with cough and fever The patient is still hospitalized, one year later, with a diagnosis of abscess of the lung It is doubtful that the injury precipitated the pathologic condition in the chest

Photographs of the fundus of the right eye taken three months after injury revealed atrophy of the optic nerve and scarring in the macular area

Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

Bacteriology and Serology

BACTERIOLOGIC STUDY OF HUMAN CONJUNCTIVAL FLORA F H
RODIN, Am J Ophth 28: 306 (March) 1945

Rodin emphasizes the value of bacteriologic study of conjunctival infections. He gives his observations in 152 cases of clinically normal conjunctivas from birth to 80 years of age. It is considered advisable to postpone operation for cataract in the presence of six or more colonies of hemolytic staphylococci or of 2 or more of hemolytic streptococci, *Pneumococcus* or *Bacillus pyocyaneus*.

W S REESE

Conjunctiva

SOME OBSERVATIONS ON THE CHEMICAL NATURE OF THE PTERYGIUM
H H BEARD and T J DIMITRY, Am J Ophth 28: 303 (March)
1945

Three pterygia were studied after surgical removal. Their average weight was about 8 mg. The chloroform-soluble material amounted to about 47.5 per cent of the fresh weight of the growth. A positive Salkowski reaction for cholesterol was obtained, but the amount present was too small to be precipitated with digitonin. The action of choline chloride in producing alterations in these growths is discussed, together with a new etiologic theory of the disease.

W S REESE

General Diseases

BILATERAL TEMPORAL ARTERITIS WITH COMPLETE LOSS OF VISION
E W SHANNON and J SOLOMON, J A M A 127: 647 (March
17) 1945

A white man aged 73 complained of severe headache and loss of vision, with severe pains in the jaws. Vision in each eye was limited to questionable perception of light. The crystalline lens showed opacities. In each eye there was edema of the retina and papilla with venous engorgement and some minute hemorrhages. A segment of the right temporal artery was removed. The vessel was grossly thrombosed. Three weeks after the operation the headache was almost entirely gone. The eyes were now blind.

In a case of bilateral temporal arteritis with complete loss of vision in both eyes, a section of one of the temporal arteries revealed the characteristic picture as described by Horton. The cause of the visual loss is not known primarily because there has been no autopsy in any of the cases of temporal arteritis. It has been suggested that the retinal artery is the site of a pathologic process similar to that described in the

temporal artery One investigator has actually worked out an anastomosis between the temporal artery and the retinal vein Other theories have been advanced

W ZENTMAYER

Glaucoma

CONGENITAL GLAUCOMA AND CATARACT, BILATERAL, GONIOTOMY AND NEEDLING T D ALLEN, *Am J Ophth* 28. 388 (April) 1945

Allen cites the case of a 5 month old child with bilateral glaucoma and an associated cataract in which he did goniotomies by inserting the goniotomy knife at the limbus of the cornea and passing it across the pupil and sweeping down into the angle in the inferior nasal quadrant Four operations were performed on the left eye No contact glass was used A single similar procedure was used on the right eye

The tension when the patient was under narcosis was 31 and 46 mm in the two eyes, this was reduced to 20 and 16 mm of mercury A single needling of the lens was done in each eye

This method is not advocated as universally applicable in all cases of deep chamber glaucoma or in all cases of hydrophthalmos, it is merely intended to record what has been accomplished in this 1 case

W ZENTMAYER

Injuries

PERFORATING OCULAR INJURIES A C SNELL JR, *Am J Ophth* 28 263 (March) 1945

In an analysis of 172 cases of perforating ocular injuries, the following factors are seen to have a reasonably consistent unfavorable influence on the chances for recovery (1) injuries with blunt objects, (2) double perforation of the globe, (3) major degrees of prolapse of the intraocular contents, (4) large intraocular hemorrhage and (5) intraocular infection On the other hand, recovery is not consistently influenced by (1) the length of the laceration, (2) the location of the laceration, (3) injury to the lens, (4) prolapse of the iris or (5) minor degrees of hemorrhage The interrelation of some of these complications is discussed The (corrected) incidence of sympathetic ophthalmia among these cases is 1.45 per cent

In the choice of methods of repair of corneal lacerations, the use of a conjunctival flap and the employment of direct corneal sutures appear to be about equally efficacious Other features in the management of perforating ocular injuries are discussed

W S REESE

Lacrimal Apparatus

DACRYOCYSTITIS THE PART PLAYED BY SYPHILIS IN ITS ETIOLOGY J O WETZEL, *Am J Ophth* 28 511 (May) 1945

In comparatively few cases of dacryocystitis has syphilis been recognized as the etiologic factor It is probable that more careful laboratory examinations might reveal many unsuspected cases Therefore it would seem desirable that serologic tests become a regular part of the examination in all cases in which the causal factor is in doubt

W S REESE

Lids

DERMATITIS OF THE LIDS FROM PENICILLIN EYE DROPS ELIAS
SELINGER, J A M A 128:437 (June 9) 1945

Various untoward reactions to penicillin have been reported in the literature. Urticaria has been observed to result from the systemic administration of the drug, and cutaneous rashes from direct contact with the substance and the solution of penicillin. In some instances the reaction was thought to be the result of contaminants rather than of the drug itself.

A man aged 53 had been treated for bilateral conjunctivitis for about one year. A solution of penicillin sodium containing 250 Oxford units of penicillin per cubic centimeter in isotonic solution of sodium chloride was prescribed, with instructions to instill 1 drop in each eye every two hours. The patient used this solution for four days, when he returned to the office because there was no improvement in the conjunctivitis. He thought a more concentrated solution might be more effective. Although at that time the skin of the upper lids seemed slightly edematous and somewhat shiny, its appearance was not accepted as an early sign of contact dermatitis, as it would have been if other medication had been used. A solution containing 500 Oxford units per cubic centimeter was prescribed. The following day the patient returned to the office with a typical picture of contact dermatitis. The skin of the lower lids was thickened, red and shiny. The redness of the lids was particularly pronounced along the side of the nose, where the excess of the solution had trickled down over the cheeks. The skin of the upper lids, especially near the inner canthi, was edematous but not red. The conjunctivas showed no reaction, and the corneas, examined with a slit lamp, were also free from reaction. A patch test gave negative results. No history of urticaria, hay fever or other allergic manifestations could be elicited. The dermatitis cleared up five days after penicillin was discontinued.

The noteworthy features of this case are the absence of any conjunctival irritation in spite of the rather pronounced dermatitis of the lids and the occurrence of the dermatitis in a person apparently not subject to allergic disturbances.

Incidentally, the results of penicillin therapy in 3 cases of acute and in 9 cases of chronic catarrhal conjunctivitis were no better than those with the older therapeutic agents.

W ZENTMAYER

Methods of Examination

THE SPACE EIKONOMETER TEST FOR ANISEIKONIA A AMES JR Am
J Ophth 28:248 (March) 1945

Ames describes the space eikonometer and the method of using it. Its use requires less time and provides an easier discriminative task for the patient than does the standard eikonometer procedure.

W S REESE

Ocular Muscles

SOME OBSERVATIONS ON DIVERGENT STRABISMUS WITH ANOMALOUS RETINAL CORRESPONDENCE H W GRANT, *Am J Ophth* 28: 472 (May) 1945

Twenty-two cases of divergent strabismus with constant anomalous correspondence were studied from the standpoint of diagnosis and treatment. The fusion was so poor in some instances as to make the after-image test unreliable.

On the basis of the therapeutic results the cases are divided into three main groups. 1 Cases with poor convergence which were incurable, the deviation tending to assume its original amount and characteristics after surgical correction. Convergence exercises helped to reduce the cosmetic defect, but the improvement was not maintained.

2 Cases with good convergence in which the deviation could be corrected surgically. Severe asthenopic symptoms and incongruous diplopia were present for years after surgical correction.

3 Cases of horror fusionis with total or partial anomalous correspondence which was completely relieved by extreme care in correcting the refractive error.

W S REESE

Pharmacology

THE EFFECT OF DETERGENT ON THE PENETRATION OF SODIUM SULPHACETAMIDE (ALBUCID SOLUBLE) INTO OCULAR TISSUES M GINSBURG and J M ROBSON, *Brit J Ophth* 29: 185 (April) 1945

The penetration of sodium sulfacetamide into the ocular tissues was studied both in living rabbits and in isolated ocular tissues. The application of the drug with a wetting agent, Duponol ME dry, increases the penetration of sodium sulfacetamide into and through the cornea. Removal of the corneal epithelium results in a great increase in the penetration of the sulfonamide drug into and through the cornea, that is, the epithelium acts as a barrier to the passage of the drug. The wetting agent does not increase the passage of the drug into the denuded cornea (i.e., the cornea with the epithelium removed). It may be concluded that the wetting agent acts by overcoming the epithelial barrier. The results suggest that addition of a wetting agent to sodium sulfacetamide is of most value with infections of the cornea and iris.

W ZENTMAYER

Retina and Optic Nerve

IODIDE THERAPY FOR SENILE MACULAR DEGENERATION R G LAIRD, *Am J Ophth* 28: 287 (March) 1945

The factors which produce senile macular degeneration are thought to be (a) senility, (b) heredity and (c) sclerosis of the choriocapillaris of the choroid. It is probable that heredity is the major factor in many instances, for it may predispose to either senility or sclerosis of the choriocapillaris.

The administration of iodides appreciably improved the vision in a majority of cases of senile macular degeneration in this series. The

mechanism by which this improvement is obtained is not known. Large doses of iodides are not necessary to obtain satisfactory results.

W S REESE

OBSERVATIONS ON RETINAL BLOOD FLOW WITH THE AID OF KUKAN'S OPHTHALMODYNAMOMETER M W MORGAN JR, J B MOHNEY and J M OLMSTED, *Am J Ophth* 28:749 (July) 1945

Application of Kukan's cup to the eye of the cat under pentobarbital anesthesia increases the intraocular pressure sufficiently to stop the blood flow in the retinal vessels.

Stimulation of the cervical sympathetic fibers increases the blood flow in the retinal vessels, probably because of the increased blood pressure outside the eyeball.

Sensory fibers in the long ciliary nerves can reflexly increase the blood flow in retinal vessels, evidently by this same mechanism, since the effect is produced when both the long and the short ciliary nerves are cut.

W S REESE

ABERRANT OPTIC NERVE FIBERS FOUND BETWEEN RETINA AND HEXAGONAL CELLS A LOEWENSTEIN, *Brit J Ophth* 29:180 (April) 1945

Two cases of aberrant nerve fibers of the optic nerve of different sizes are described. The first type was found in a case of pigmented tumor of the optic disk infiltrating the neighboring retina and choroid. The lesion is assumed to be a malignant degeneration of a pigmented nevus of the optic disk. This type involves maldevelopment of the posterior retinal layers in front of the growth. The second type was seen in a case of hypertensive retinopathy with edematous swelling of the papilla and a large druse. The nerve fiber tissue found between the retina and the pigmented epithelium was degenerated in a ganglioform manner. The retina in front of this tissue was well developed. A mechanical pushing out of the optic nerve fibers, due to the edema and the pressure of the druse, is assumed to be the cause.

The article is illustrated.

W ZENTMAYER

Tumors

ERRORS IN DIAGNOSIS OF INTRAOCULAR TUMORS W E BRUNER, *Am J Ophth* 28:297 (March) 1945

Bruner reports 7 cases of intraocular tumor and discusses them from the standpoint of diagnosis, management and final outcome.

W S REESE

News and Notes

UNIVERSITY NEWS

Ophthalmologic Seminar, Emory University School of Medicine — Emory University School of Medicine will celebrate the one-hundredth anniversary of the birth of Abner Wellborn Calhoun, L.D. LL.D., who was born April 16, 1845 and died Aug 21 1910 the first professor of ophthalmology of the Atlanta Medical College

You are cordially invited to be the guest of Emory University at an ophthalmologic seminar to be held in Atlanta, Ga April 4 5 and 6, 1946

The following papers will be presented

April 4 Evening "Myasthenia Gravis," Dr Frank B Walsh
"Medical Ophthalmology," Dr Walter I Lillie

April 5 Morning "Diplopia," Dr Walter I Lillie, "Clinical Meaning of Exophthalmos," Dr William Benedict

Afternoon "Ocular Changes in Diabetes," Dr Derrick Vail, "Nasopharyngeal Tumors," Dr Frank B Walsh

Evening "Ocular Therapeutics in Glaucoma," Dr Parker Heath, "Treatment of Detachment of the Retina," Dr John Dunnington

April 6 Morning "Glaucoma in Diabetes," Dr William Benedict, "Surgical Treatment of the Vertical Deviations," Dr John Dunnington

Afternoon "Random Notes on Ocular Surgery," Dr Parker Heath
"Ocular Signs of Subdural Hematoma," Dr Frank B Walsh, "Clinical Diagnosis of Retinobulbar Neuritis," Dr Walter I Lillie

Evening "Preparation of the Patient for Cataract Operation," Dr William Benedict, "Circulation of the Optic Nerve and Its Influence on Disease," Dr Derrick Vail

For further information, address Dr Eugene Stead, Dean, 50 Armstrong Street, S.E. Atlanta, Ga

GENERAL NEWS

American Orthoptic Council Examinations for Technicians — The next examination by the American Orthoptic Council will be held in September and October 1946

The written examinations will be held at various cities in the country on Friday, September 6 Only those passing the written examinations will be permitted to take the oral and practical tests, to be given in Chicago, Saturday, October 12

Applications on official forms must be received before July 1, 1946

Address the American Orthoptic Council, 23 East Seventy-ninth Street, New York 21

Oregon Academy of Ophthalmology and Otolaryngology — The sixth annual spring postgraduate course in ophthalmology and otolaryngology will be held in Portland, Ore, April 15 to 20, 1946 Dr Algernon B Reese, professor of ophthalmology, Columbia University, New York, and Dr Gabriel Tucker, professor of bronchoscopy and laryngology, University of Pennsylvania Graduate School, Philadelphia, will be guest speakers

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Secretary Dr C K Lin, 180 Hsi-Lo-yen Chienmeng, Peiping
Place Peiping Union Medical College, Peiping Time Last Friday of each month

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date

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 All correspondence should be addressed to the Assistant Secretary

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President Dr W Niccol, 4 College Green, Gloucester, England
 Secretary Mr T Harrison Butler, 61 Newhall St, Birmingham 3, England
 Place Birmingham and Midland Eye Hospital

NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President Mr E F Wilson, 24 Upper Northgate St, Chester
 Secretary Mr William M Muirhead, 70 Upper Hanover St, Sheffield 3
 Place Manchester, Leeds, Newcastle-upon-Tyne, Liverpool, Sheffield and Bradford,
 in rotation Time October to May

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President Dr J Ringland Anderson, Astor House, 108 Collins St, Melbourne, Victoria
 Secretary Dr D A Williams, 27 Commonwealth St, Sydney
 Place Melbourne Time Oct 20-26, 1946

OPHTHALMOLOGICAL SOCIETY OF EGYPT

President Prof Dr Mohammed Malifouz Bey, Government Hospital, Alexandria
 Secretary Dr Mohammed Khalil, 4 Baehler St, Cairo
 All correspondence should be addressed to the secretary, Dr Mohammed Khalil

OPHTHALMOLOGICAL SOCIETY OF HOSPITAL DE NUESTRA SEÑORA DE LA LUZ

Chairman Dr Manuel J Icaza y Dublan, Mexico, D F, Mexico
 Secretary Dr Jorge Meyran, Mexico, D F, Mexico

OPHTHALMOLOGICAL SOCIETY OF SOUTH AFRICA

President Dr A W Sichel, National Mutual Bldg, Church Square, Cape Town
 Secretary Dr J K de Kock, Groote Kerk Bldg, 32 Parliament St, Cape Town

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President Mr Charles B Goulden, 89 Harley St, London
 Secretary Mr Frank W Law, 30 Devonshire Pl, London, W 1

OPHTHALMOLOGY SOCIETY OF BOMBAY

President Dr D D Sathaye, 127 Girgaum Rd, Bombay 4, India
 Secretary Dr H D Dastur, Dadar, Bombay 14, India
 Place H B A Free Ophthalmic Hospital, Parel, Bombay 12 Time First
 Friday of every month

OXFORD OPHTHALMOLOGICAL CONGRESS

Master Mr P G Doyne, 60 Queen Anne St, London, W 1, England
 Secretary-Treasurer Dr F A Anderson, 12 St John's Hill, Shrewsbury, England
 Time July 4-6, 1946

PALESTINE OPHTHALMOLOGICAL SOCIETY

President Dr Arieh Feigenbaum, Abyssinian St 15, Jerusalem
 Secretary Dr E Sinai, Tel Aviv

POLISH OPHTHALMOLOGICAL SOCIETY

President Dr W Kapuściński, 2 Waly Batorego, Poznań
 Secretary Dr J Sobański, Lindley'a 4, Walsaw
 Place Lindley'a 4, Warsaw

ROYAL SOCIETY OF MEDICINE, SECTION OF OPHTHALMOLOGY

President Col F A Juler, 96 Harley St, London, W 1, England
 Secretary Dr Harold Ridley, 60 Queen Anne St, London, W 1, England

SÃO PAULO SOCIETY OF OPHTHALMOLOGY

President Silvio de Almeida Toledo, Barão de Ilapetininga St, 88, 5° Andar,
 São Paulo, Brazil
 Secretary Dr Plinio de Toledo Piza, Enfermaria Santo Luzia, Santa Casa de
 Misericórdia, Cesario Motta, St 112, São Paulo, Brazil

SCOTTISH OPHTHALMOLOGICAL CLUB

President Dr S Spence Meighan, 13 Woodside Pl, Glasgow, C 3
 Secretary Dr Alexander Garrow, 15 Woodside Pl, Glasgow, C 3
 Place Edinburgh and Glasgow, in rotation

SOCIEDAD ARGENTINA DE OFTALMOLOGIA

Chairman Dr Jorge Malbran, Buenos Aires
 Secretary Dr Benito Just Tiscornia, Santa Fe 1171, Buenos Aires

SOCIEDAD OFTALMOLOGIA DEL LITORAL, ROSARIO (ARGENTINA)

President Prof Dr Carlos Weskamp, Laprida 1159, Rosario
 Secretary Dr Arturo Etchemendigaray, Villa Constitucion, Santa Fe
 Place Rosario Time Last Saturday of every month, April to November All
 correspondence should be addressed to the President

SOCIEDADE DE OFTALMOLOGIA DEL NORTE

President Dr Alberto Cardenas
 Secretary Dr Jorge Luis Castillo, Mendoza 421, Tucumán, Argentina

SOCIEDADE DE OFTALMOLOGIA DE MINAS GERAIS

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 Geraes, Brazil
 Secretary Dr Ennio Coscarelli, Rua Aimores 1697, Bello Horizonte, Minas Geiaes,
 Brazil

SOCIEDADE DE OFTALMOLOGIA E OTORRINOLARINGOLOGIA DE
 RIO GRANDE DO SUL

President Dr Luiz Assumpção Osorio, Edificio Vera Cruz, Apartamento 134,
 Porto Alegre, Rio Grande do Sul
 Secretary Dr Fernando Voges Alves, Caixa Postal 928, Porto Alegre, Rio Grande
 do Sul

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Secretary Dr Adroaldo de Alencar, Brazil

All correspondence should be addressed to the President

SOCIETÀ OTTALMOLOGICA ITALIANA

President Prof Dott Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome

Secretary Prof Dott Epimaco Leonardi, Via del Gianicolo, 1, Rome

SOCIÉTÉ FRANÇAISE D'OPHTHALMOLOGIE

Secretary Dr René Onfray, 6 Avenue de la Motte Picquet, Paris, 7^e

SOCIETY OF SWEDISH OPHTHALMOLOGISTS

President Prof K G Ploman, Stockholm

Secretary Dr K O Granström, Södermalmstorg 4, III tr, Stockholm, So

TEL AVIV OPHTHALMOLOGICAL SOCIETY

President Dr D Arich-Friedman, 96 Allenby St, Tel Aviv, Palestine

Secretary Dr Sadger Ma'., 9 Bialik St, Tel Aviv, Palestine

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION
ON OPHTHALMOLOGY

Chairman Dr Frederick C Cordes, 384 Post St, San Francisco

Secretary Dr R J Masters, 23 E Ohio St, Indianapolis

Place San Francisco Time July 1-5, 1946

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY,
SECTION ON OPHTHALMOLOGY

President Dr Gordon B New, Mayo Clinic, Rochester, Minn

President-Elect Dr Alan C Woods, Johns Hopkins Hospital, Baltimore 5

Executive Secretary-Treasurer Dr William L Benedict, 100-1st Ave Bldg,
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President Dr Alexander E MacDonald, 170 St George St, Toronto 5

Secretary-Treasurer Dr L J Sebert, 170 St George St, Toronto 5

CANADIAN OPHTHALMOLOGICAL SOCIETY

President Walter W Wright, 170 St George St, Toronto 5

Secretary-Treasurer Dr Kenneth B Johnston, Suite 1, 1509 Sherbrooke St W,
Montreal

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS

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 Secretary Miss Regina E Schneider, 1790 Broadway, New York
 Executive Director Mrs Eleanor Brown Merrill, 1790 Broadway, New York

SECTIONAL

ACADEMY OF MEDICINE OF NORTHERN NEW JERSEY, SECTION ON
 EYE, EAR, NOSE AND THROAT

President Dr N Zwaifler, 46 Wilbur Ave, Newark
 Secretary Dr William F Keim Jr, 25 Roseville Ave Newark
 Place 91 Lincoln Park South, Newark Time 8 45 p m, second Monday of
 each month, October to May

CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Watson Gailey, 1000 N Main St, Bloomington, Ill
 Secretary-Treasurer Dr William F Hubble, 861-867 Citizens Bldg, Decatur, Ill

CENTRAL WISCONSIN SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr L J Friend, 425 E Grand Ave, Beloit, Wis
 Secretary Dr G L McCormick, 626 S Central Ave, Marshfield

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President Dr Theodore L Terry, 140 Marlborough St, Boston
 Secretary-Treasurer Dr Merrill J King, 264 Beacon St, Boston 16
 Place Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston Time
 8 p m, third Tuesday of each month from November to April, inclusive

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President Dr D H O'Rourke, 1612 Tremont Pl, Denver
 Secretary-Treasurer Dr C Allen Dickey, 450 Sutter St, San Francisco

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr James H Mathews, 1317 Marion St, Seattle, Wash
 Secretary-Treasurer Dr Barton E Peden, 301 Stimson Bldg, Seattle 1
 Place Seattle or Tacoma, Wash Time Third Tuesday of each month except
 June, July and August

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President Dr J Sheldon Clark, 27 E Stephenson St, Freeport, Ill
 Secretary-Treasurer Dr Harry R Warner, 321 W State St, Rockford, Ill
 Place Rockford, Ill, or Janesville or Beloit, Wis Time Third Tuesday of each
 month from October to April, inclusive

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr L D Gomon, 308 Eddy Bldg, Saginaw, Mich
 Secretary-Treasurer Dr Harold H Heuser, 207 Davidson Bldg, Bay City, Mich
 Place Saginaw or Bay City, Mich Time Second Tuesday of each month, except
 July, August and September

SIoux VALLEY EYE AND EAR ACADEMY

President Dr J C Decker, 515 Francis Bldg, Sioux City, Iowa
 Secretary-Treasurer Dr J E Dvorak, 408 Davidson Bldg, Sioux City, Iowa

SOUTHERN MEDICAL ASSOCIATION, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman Dr John H Burleson, 414 Navarro St, San Antonio, Texas

Secretary Dr J W Jervey Jr, 101 Church St, Greenville, S C

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President Dr H L Brehmer, 221 W Central Ave, Albuquerque, N Mex

Secretary Dr A E Cruthirds, 1011 Professional Bldg, Phoenix, Ariz

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President Dr W M Dodge, 716 First National Bank Bldg, Battle Creek

Secretary-Treasurer Dr Kenneth Lowe, 25 W Michigan Ave, Battle Creek

Time Last Thursday of September, October, November, March, April and May

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Ray Parker, 218 Franklin St, Johnstown, Pa

Secretary-Treasurer Dr J McClure Tyson, Deposit National Bank Bldg, Dubois

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President Dr Raymond C Cook, 701 Main St, Little Rock

Secretary Dr K W Cosgrove, Urquhart Bldg, Little Rock

COLORADO OPHTHALMOLOGICAL SOCIETY

President Dr C A Ringle, 912-9th Ave, Greeley

Secretary Dr W A Ohmart, 1102 Republic Bldg, Denver

Place University Club, Denver Time 7 30 p m, thrd Saturday of each month,
October to May, inclusiveCONNECTICUT STATE MEDICAL SOCIETY, SECTION ON EYE, EAR,
NOSE AND THROAT

President Dr F L Phillips, 405 Temple St, New Haven

Secretary-Treasurer Dr W H Turnley, 1 Atlantic St, Stamford, Conn

EYE, EAR, NOSE AND THROAT CLUB OF GEORGIA

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Secretary-Treasurer Dr C K McLaughlin, 526 Walton St, Macon

INDIANA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr F McK Ruby, Union City

Secretary Dr Edwin W Dyar Jr, 23 E Ohio St, Indianapolis

Place French Lick Time First Wednesday in April

IOWA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr J K Von Lackum, 117-3d St S E, Cedar Rapids

Secretary-Treasurer Dr B M Merkel, 604 Locust St, Des Moines

KANSAS STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY AND
OTOLARYNGOLOGY

President Dr W D Pittman, Pratt

Secretary Dr Louis R Haas, 902 N Broadway, Pittsburg

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr Val H Fuchs, 200 Carondelet St, New Orleans

Secretary-Treasurer Dr Edley H Jones, 1301 Washington St, Vicksburg, Miss

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, SECTION ON
EYE, EAR, NOSE AND THROAT DISEASES

Chairman Dr William T Hunt Jr, 1205 Spruce St, Philadelphia 7
Secretary Dr Gabriel Tucker, 250 S 18th St, Philadelphia 3

MICHIGAN STATE MEDICAL SOCIETY, SECTION OF OPHTHALMOLOGY
AND OTOLARYNGOLOGY

Chairman Dr Edmond L Cooper, 1553 Woodward Ave, Detroit 26
Secretary Dr Ralph H Gilbert, 110 Fulton St E, Grand Rapids

MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Karl C Wold, 1051 Lowry Bldg, St Paul 2
Secretary Dr William A Kennedy, 372 St Peter St, St Paul 2
Time Second Friday of each month from October to May

MONTANA ACADEMY OF OTO-OPHTHALMOLOGY

President Dr William Morrison, 208 N Broadway, Billings
Secretary Dr Fritz D Hurd, 309 Medical Arts Bldg, Great Falls

NEBRASKA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha
Secretary-Treasurer Dr John Peterson, 1307 N St, Lincoln

NEW JERSEY STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY,
OTOLOGY AND RHINOLARYNGOLOGY

Chairman Dr George P Meyer, 410 Haddon Ave, Camden
Secretary Dr John P Brennan, 429 Cooper St, Camden

NEW YORK STATE MEDICAL SOCIETY, EYE, EAR, NOSE
AND THROAT SECTION

Chairman Dr Harold J Joy, 504 State Tower Bldg, Syracuse 2
Secretary Dr Maxwell D Ryan, 660 Madison Ave, New York 21

NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Hugh C Wolfe, 102 N Elm St, Greensboro
Secretary Dr Vanderbilt F Couch, 104 W 4th St, Winston-Salem

NORTH DAKOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr W L Diven, City National Bank Bldg, Bismarck
Secretary-Treasurer Dr A E Spear, 20 W Villard, Dickinson

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Paul Neely, 1020 S W Taylor St, Portland
Secretary-Treasurer Dr Harold M U'Ren, 624 Medical Arts Bldg, Portland 5
Place Good Samaritan Hospital, Portland Time Third Tuesday of each month

PENNSYLVANIA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Lewis T Buckman, 83 S Franklin St, Wilkes-Barre
Secretary Pro Tem Dr Paul C Craig, 232 N 5th St, Reading
Time Last week in April

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President Dr N Darrell Harvey, 112 Waterman St, Providence
 Secretary-Treasurer Dr Linley C Happ, 124 Waterman St, Providence
 Place Rhode Island Medical Society, Library, Providence Time 8 30 p m,
 second Thursday in October, December, February and April

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr J H Stokes, 125 W Cheves St, Florence
 Secretary-Treasurer Dr Roderick Macdonald, 330 E Main St, Rock Hill

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Wesley Wilkerson, 700 Church St, Nashville
 Secretary-Treasurer Dr W D Stinson, 124 Physicians and Surgeons Bldg,
 Memphis

TEXAS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr F H Rosebrough, 603 Navarro St, San Antonio
 Secretary Dr M K McCullough, 1717 Pacific Ave, Dallas

UTAH OPHTHALMOLOGICAL SOCIETY

President Dr E B Fairbanks, 315 Medical Arts Bldg, Salt Lake City
 Secretary-Treasurer Dr Dean Spear, 516 Boston Bldg, Salt Lake City
 Place University Club, Salt Lake City Time 7 00 p m, third Monday of
 each month

VIRGINIA SOCIETY OF OTOLARYNGOLOGY AND OPHTHALMOLOGY

President Dr Mortimer H Williams, 30½ Franklin Rd S W, Roanoke
 Secretary-Treasurer Dr Meade Edmunds, 34 Franklin St, Petersburg

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND
THROAT SECTION

President Dr George Traugh, 309 Cleveland Ave, Fairmont
 Secretary Dr Welch England, 621½ Market St, Parkersburg

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr E L Mather, 39 S Main St, Akron, Ohio
 Secretary-Treasurer Dr V C Malloy, 2d National Bank Bldg, Akron, Ohio
 Time First Monday in January, March, May and November

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr B M Cline, 153 Peachtree St N E, Atlanta, Ga
 Acting Secretary Dr A V Hallum, 478 Peachtree St N E, Atlanta, Ga
 Place Grady Hospital Time 6 00 p m, fourth Monday of each month from
 October to May

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman Dr Ernst Bodenheimer, 1212 Eutaw Pl, Baltimore
 Secretary Dr Thomas R O'Rourke, 104 W Madison St, Baltimore
 Place Medical and Chirurgical Faculty, 1211 Cathedral St Time 8 30 p m,
 fourth Thursday of each month from October to March

BIRMINGHAM EYE, EAR, NOSE AND THROAT CLUB

President Each member, in alphabetical order
 Secretary Dr Luther E Wilson, 919 Woodward Bldg, Birmingham, Ala
 Place Tutwiler Hotel Time 6 30 p m, second Tuesday of each month, September to May, inclusive

BROOKLYN OPHTHALMOLOGICAL SOCIETY

President Dr Michael J Buonaguro, 589 Lorimer St, Brooklyn 11
 Secretary-Treasurer Dr Louis Freimark, 256 Rochester Ave, Brooklyn 13
 Place Kings County Medical Society Bldg, 1313 Bedford Ave Time Third Thursday in February, April, May, October and December

BUFFALO OPHTHALMOLOGIC CLUB

President Dr William H Howard, 389 Linwood Ave, Buffalo 9
 Secretary-Treasurer Dr Sheldon B Freeman, 196 Linwood Ave, Buffalo 9
 Time Second Thursday of each month from October to May

CHATTANOOGA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Each member, in alphabetical order
 Secretary Dr Douglas Chamberlain, Chattanooga Bank Bldg, Chattanooga, Tenn
 Place Mountain City Club Time Second Thursday of each month from September to May

CHICAGO OPHTHALMOLOGICAL SOCIETY

President Dr Samuel J Meyer, 58 E Washington St, Chicago 2
 Secretary Dr W A Maun, 30 N Michigan Ave, Chicago 2
 Place Continental Hotel, 505 N Michigan Ave Time Third Monday of each month from October to May

CINCINNATI GENERAL HOSPITAL OPHTHALMOLOGY STAFF

Chairman Dr D T Vail, 441 Vine St, Cincinnati
 Secretary Dr A A Levin, 441 Vine St, Cincinnati
 Place Cincinnati General Hospital Time 7 45 p m, third Friday of each month except June, July and August

CLEVELAND OPHTHALMOLOGICAL CLUB

Chairman Dr M Paul Motto, Rose Bldg, Cleveland
 Secretary Dr H H Wygand, Guardian Bldg, Cleveland
 Time Second Tuesday in October, December, February and April

COLLEGE OF PHYSICIANS, PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Chairman Dr W S Reese, 1901 Walnut St, Philadelphia
 Clerk Dr George F J Kelly, 37 S 20th St, Philadelphia
 Time Third Thursday of every month from October to April, inclusive

COLUMBUS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

Chairman Dr Erwin W Troutman, 21 E State St, Columbus, Ohio
 Secretary-Treasurer Dr T Rees Williams, 380 E Town St, Columbus 15, Ohio
 Place University Club Time 6 15 p m, first Monday of each month, from October to May, inclusive

CORPUS CHRISTI EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Dr C B Collins, 704 Medical Professional Bldg, Corpus Christi, Texas
 Secretary Dr L W O Janssen, 710 Medical Professional Bldg, Corpus Christi, Texas
 Time 6 30 p m, third Tuesday of each month from October to May

DALLAS ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Ruby K Daniel, Medical Arts Bldg, Dallas 1, Texas

Secretary Dr Tom Barr, Medical Arts Bldg, Dallas 1, Texas

Place Dallas Athletic Club Time 6 30 p m, first Tuesday of each month from October to June The November, January and March meetings are devoted to clinical work

DES MOINES ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr H C Schmitz, 604 Locust St, Des Moines, Iowa

Secretary-Treasurer Dr Byron M Merkel, 604 Locust St, Des Moines, Iowa

Time 7 45 p m, third Monday of every month from September to May

DETROIT OPHTHALMOLOGICAL CLUB

Chairman Members rotate alphabetically

Secretary Dr Wesley G Reid, 667 Fisher Bldg, Detroit 2

Place Club rooms of Wayne County Medical Society Time First Monday of each month, November to April, inclusive

DETROIT OPHTHALMOLOGICAL SOCIETY

President Dr Raymond S Goux, 545 David Whitney Bldg, Detroit 26

Secretary Dr Arthur Hale, 1609 Eaton Tower, Detroit 26

Place Club rooms of Wayne County Medical Society Time 6 30 p m, third Thursday of each month from November to April, inclusive

EASTERN NEW YORK EYE, EAR, NOSE AND THROAT ASSOCIATION

President Appointed at each meeting

Secretary-Treasurer Dr Joseph L Holohan, 330 State St, Albany

Time Third Wednesday in October, November, March, April, May and June

FORT WORTH EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Rex Howard, 602 W 10th St, Fort Worth, Texas

Secretary-Treasurer Dr R H Gough, Medical Arts Bldg, Fort Worth, Texas

Place Medical Hall, Medical Arts Bldg Time 7 30 p m, first Friday of each month except July and August

HOUSTON ACADEMY OF MEDICINE, OPHTHALMOLOGICAL AND
OTO-LARYNGOLOGICAL SECTION

President Dr Lyle J Logue, 1304 Walker Ave, Houston, Texas

Secretary Dr John T Stough, 803 Medical Arts Bldg, Houston, Texas

Place Medical Arts Bldg, Harris County Medical Society Rooms Time 8 p m, second Thursday of each month from September to June

INDIANAPOLIS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr Myron Harding, 23 E Ohio St, Indianapolis

Secretary Dr Kenneth L Craft, 23 E Ohio St, Indianapolis

Place Indianapolis Athletic Club Time 6 30 p m, second Thursday of each month from November to May

KANSAS CITY SOCIETY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Edgar Johnson, 906 Grand Ave, Kansas City, Mo

Secretary Dr W E Keith, 1103 Grand Ave, Kansas City, Mo

Time Third Thursday of each month from October to June The November, January and March meetings are devoted to clinical work

LONG BEACH EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Dr Francis Carl Hertzog, 117 E 8th St, Long Beach, Calif
 Secretary-Treasurer Dr Robert G Thornburgh, 117 E 8th St, Long Beach, Calif
 Place Seaside Hospital Time Last Wednesday of each month from October to May

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Orrie E Ghrist, 210 N Central Ave, Glendale, Calif
 Secretary-Treasurer Dr K C Brandenburg, 110 Pine Ave, Long Beach 2, Calif
 Place Los Angeles County Medical Association Bldg, 1925 Wilshire Blvd Time
 6 30 p m, fourth Monday of each month from September to May, inclusive

LOUISVILLE EYE AND EAR SOCIETY

President Dr Joseph S Heitger, Heyburn Bldg, Louisville, Ky
 Secretary-Treasurer Dr J W Fish, 321 W Broadway, Louisville, Ky
 Place Brown Hotel Time 6 30 p m, second Thursday of each month from September to May, inclusive

LOWER ANTHRACITE EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Each member in alphabetical order
 Secretary Dr James J Monohan, 31 S Jardin St, Shenandoah, Pa

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION OF
 OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Dr P S Constantinople, 1835 I St N W, Washington
 Secretary Dr Frazier Williams, 1801 I St N W, Washington
 Place 1718 M St N W Time 8 p m, third Friday of each month from October to April, inclusive

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Each member, in alphabetical order
 Secretary Dr Sam H Sanders, 1089 Madison Ave, Memphis, Tenn
 Place Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital Time 8 p m,
 second Tuesday of each month from September to May

MILWAUKEE OTO-OPHTHALMIC SOCIETY

President Dr Ralph T Rank, 238 W Wisconsin Ave, Milwaukee
 Secretary-Treasurer Dr Frank G Treskow, 411 E Mason St, Milwaukee 2
 Place University Club Time 6 30 p m, fourth Tuesday of each month from October to May

MONTGOMERY COUNTY MEDICAL SOCIETY

Chairman Dr H V Dutrow, 1040 Fidelity Medical Bldg, Dayton, Ohio
 Secretary-Treasurer Dr Maitland D Place, 981 Reibold Bldg, Dayton, Ohio
 Place Van Cleve Hotel Time 6 30 p m, first Tuesday of each month from October to June, inclusive

MONTREAL OPHTHALMOLOGICAL SOCIETY

President Dr J Rosenbaum, 1396 Ste Catherine St W, Montreal, Canada
 Secretary Dr L Tessier, 1230 St Joseph Blvd E, Montreal, Canada
 Time Second Thursday of October, December, February and April

NASHVILLE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Dr M M Cullom, 700 Church St, Nashville, Tenn
 Secretary Dr R E Sullivan, 432 Doctors Bldg, Nashville, Tenn
 Place James Robertson Hotel Time 6 30 p m, third Monday of each month from October to May

NEW HAVEN OPHTHALMOLOGICAL SOCIETY

President Dr William H Ryder, 185 Church St, New Haven, Conn
 Secretary Dr Frederick A Wiess, 255 Bradley St, New Haven, Conn

NEW ORLEANS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr W B Clark, 1012 American Bank Bldg, New Orleans
 Secretary Dr Mercer G Lynch, 1018 Maison Blanche Bldg, New Orleans
 Place Louisiana State University Medical Bldg Time 8 p m, second Tuesday
 of each month from October to May

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman Dr Rudolf Aebli, 30 E 40th St, New York
 Secretary Dr Truman L Boyes, 654 Madison Ave, New York
 Time 8 30 p m, third Monday of every month from October to May, inclusive

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President Dr Maurice L Wieselthier, 1322 Union St, Brooklyn
 Secretary Dr Benjamin Esterman, 983 Park Ave, New York 28
 Place New York Academy of Medicine, 2 E 103d St Time 8 p m, first Monday
 of each month from October to May, inclusive

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Harvey O Randel, 117 N Broadway, Oklahoma City
 Secretary Dr S R Shaver, 117 N Broadway, Oklahoma City
 Place University Hospital Time Second Tuesday of each month from Sep-
 tember to May

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND
OTO-LARYNGOLOGICAL SOCIETY

President Dr A A Steinberg, 1502 Farnam St, Omaha
 Secretary-Treasurer Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha 2
 Place Omaha Club, 20th and Douglas Sts, Omaha Time 6 p m dinner, 7 p m
 program, third Wednesday of each month from October to May

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President Dr Thomas Sanfacon, 340 Park Ave, Paterson, N J
 Secretary-Treasurer Dr J Averbach, 435 Clinton Ave, Clinton, N J
 Place Paterson Eye and Ear Infirmary Time 9 p m, last Friday of every
 month, except June, July and August

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

President Dr Isaac Tassman, 136 S 16th St, Philadelphia
 Secretary Dr Glen Gregory Gibson, 255 S 17th St, Philadelphia
 Time First Thursday of each month from October to May

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

President Dr Clarence F Bernatz, Park Bldg, Pittsburgh
 Secretary Dr Robert J Billings, Park Bldg, Pittsburgh
 Place Pittsburgh Academy of Medicine Bldg Time Fourth Monday of each
 month, except June, July, August and September

READING EYE, EAR, NOSE AND THROAT SOCIETY

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 Secretary Dr Paul C Craig, 232 N 5th St, Reading, Pa
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 Aviation Cadet Center Time 7 p m , second Tuesday of each month from
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 Secretary-Treasurer Dr I H Blaisdell, 713 E Genesee St , Syracuse, N Y
 Place University Club Time First Tuesday of each month except June, July
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 Place Toledo Club Time Each month except June, July and August

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Place Academy of Medicine, 13 Queens Park Time First Monday of each month, November to April

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PARALYSIS OF OCULAR ELEVATION WITH AND WITHOUT PTOSIS

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NEW YORK

VARIOUS conditions of paralysis of ocular elevation with and without ptosis will be described and cases illustrating the different types according to the muscles paralyzed will be reported. The purpose of this paper is to differentiate real ptosis and pseudoptosis and to bring out the indications for the application and the technic of surgical procedures which may be useful in correcting the hypotropia of the paretic eye, or the hypertropia of the sound, or fellow, eye when the patient prefers to fix with the paretic eye, and, finally, in correcting the ptosis.

DEFINITIONS

Under the term "paralysis of ocular elevation" may be grouped a number of cases of disturbed ocular motility in which it is difficult or impossible for the patient to look upward because of the paralysis of the superior rectus and/or the inferior oblique muscle. For the sake of simplicity, the word "ptosis" in this paper signifies blepharoptosis. There may be associated either real ptosis or pseudoptosis. By real ptosis is meant a condition caused by paralysis of the levator muscle and/or the smooth muscle of the eyelid. By pseudoptosis is meant not a spastic closure of the lids by the orbicularis muscle but a lowered position of the upper eyelid associated with hypotropia. There are signs, such as a crease and fold in the upper eyelid, indicating the attachment of an active levator muscle to the skin, and the ability to open the eye when the fellow eye is occluded, that the levator and the smooth muscle are not paralyzed.

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I acknowledge the contributions and teachings of Dr. J. M. Wheeler and Dr. James White in this field of study of ocular motility and the assistance of Dr. White in reviewing and criticizing this paper.

Read at a meeting of the New York Academy of Medicine, Section of Ophthalmology, March 19, 1945, and at the Eighty-First Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., Nov. 12, 1945.

SIMPLE PARALYSES OF OCULAR ELEVATION WITH
OR WITHOUT PTOSIS

PTOSIS WITHOUT PARALYSIS OF ELEVATION

If partial or complete paralysis of the levator palpebrae superioris and/or the smooth muscle of the upper eyelid results in ptosis and there are no coincident or complicating paralyses of the extrinsic ocular muscles, particularly of the superior rectus or the inferior oblique, then the conclusions previously arrived at¹ for the surgical correction of ptosis still apply

1 Skin or subcutaneous tissue should not be removed unless it is in excess of normal or unless there is inflammatory thickening or cicatricial tissue which interferes with action of the lid. The production of deep cicatrices or sclerosis of tissue for the correction of ptosis is contraindicated. Lagophthalmos should be avoided. The orbicularis, particularly, should be preserved to assist in closure of the eye.

2 If the paralysis of the muscles of the lid is partial, the palpebral fissure being wider in elevation than in depression of the eye, and there is visible a crease or fold in the upper lid as evidence of attachment and activity of the muscles of the lid, then the principle of resection and advancement of the levator and the smooth muscle of the upper lid and resection of a portion of the tarsus is indicated.

3 If there is complete, or almost complete, paralysis of the levator and smooth muscle of the upper lid, with complete ptosis and a flat, expressionless lid, the palpebral fissure is actually narrower in elevation than in depression of the eye and there is no paralysis of the elevator muscles of the eye, then the Motais principle of transplantation of a portion of the superior rectus muscle is indicated.

4 The indications for the employment of the frontalis muscle, to enhance its vicarious action in certain cases of ptosis, are brought out later in this paper. In general it may be said that the patient wishes to get rid of the arching of the brows, the corrugation of the forehead and the peculiar facial expression. This is his expression of ptosis, and he does not wish it continued by a frontalis muscle operation if this could be avoided by an operation on the levator and tarsus or the superior rectus when such a procedure is indicated and feasible.

PARALYSIS OF SUPERIOR RECTUS MUSCLE WITHOUT PTOSIS

Paralysis may affect the superior rectus muscle alone. In such a case there may be overaction or spasm of the inferior oblique muscle of the fellow eye when the eye with the paretic superior rectus is

1 Kirby, D. B. Blepharoptosis. The Technique of Its Surgical Correction, Surg., Gynec. & Obst. 70 438-449, 1940

fixing This condition may be unilateral or bilateral In case of unilateral paralysis the patient may, and usually does, exhibit a deviation of the sound, or fellow, eye upward and in the field of action of the interior oblique muscle when he chooses to fix with the eye that has the paretic superior rectus muscle This phenomenon may be explained in one of two ways First, the nervous stimulation directed to the paretic muscle may be more than necessary, and the reaction of the inferior oblique muscle, which acts in the same field for the fellow eye, is correspondingly greater, or, second, diplopia and confusion occur in the fields of action of the paretic superior rectus and the sound inferior oblique of the fellow eye, and various efforts are made to avoid the accompanying confusion The overaction or spasm of the inferior oblique may accomplish this, moving the second image farther away from the first image Some patients tilt and rotate their heads, either to avoid diplopia or to hold fusion in a limited field In case there is paralysis of the superior rectus muscle of each eye there may be found double hyperphoria or hypertropia, particularly when fixation is made alternately in the field of action of the paralyzed superior rectus muscles For example, when, with the right eye fixing, the eyes are turned up and to the right, there will be left hyperphoria or hypertropia, due to the secondary deviation of the left inferior oblique, and the reverse will be true when the left eye is fixing in the position of eyes left Variations in the degree of deviation will depend on whether or not the superior rectus muscles are equally paralyzed and whether or not the inferior oblique muscles are equally overactive The picture will also vary with the presence or absence of binocular single vision This usually depends on the age at which the paralysis developed Many such conditions and illustrative cases have previously been described The indications for and the application of surgical procedures in such cases are well known It is unwise to resect or advance the paretic superior rectus because the patient will continue to fix with the paretic eye and the secondary deviation of the fellow eye will remain The condition of paralysis of one or both superior rectus muscles with accompanying spasm of the inferior oblique of the fellow eye, with or without ocular torticollis, has been satisfactorily alleviated by myotomy (previously called tenotomy) or myectomy of the overactive inferior oblique at its origin, the choice depending on the degree of the deviation Myotomy or myectomy at the insertion of the inferior oblique usually results in complete paralysis of the muscle The application of the principle of recession of the inferior oblique from its insertion, as developed by White,² has given more accurate results, particularly

2 White, J W Surgery of Inferior Oblique At or Near the Insertion, *Am. J Ophth* 26 586-591, 1943

in cases of lesser degrees of paralysis and in cases of bilateral involvement in which a graduated effect is desirable in order to obtain a horizontal level of the two eyes in the primary position

UNILATERAL PARALYSIS OF SUPERIOR RECTUS MUSCLE
WITH COMPLETE PTOSIS BUT WITH INTACT
INFERIOR OBLIQUE MUSCLE

In a case of ptosis there may be evidence of paralysis of the superior rectus muscle but with an intact inferior oblique muscle

It has often been said that in the presence of a paralyzed superior rectus muscle and complete real ptosis the Motais principle of transplantation of a portion of the superior rectus muscle for relief of the ptosis should not be employed. The decision should rest on whether the eye on the affected side is level with the fellow eye in the primary position, whether there are other signs or tests of activity of the inferior oblique of the same eye, such as absence of diplopia when the eye is turned into the plane of action of its inferior oblique, and whether the excursion and the screen test in the six cardinal positions indicate the paralysis of the superior rectus and the levator muscle only. If in application of other tests which should be used in a case of ptosis it is found (1) that the paralysis of the levator muscle of the eyelid is practically complete and the procedure of resection and advancement of the levator and tarsus would fail, (2) that the palpebral fissure is actually narrower on elevation than on depression of the eyes, and (3) that, in addition, the patient can roll the affected eye up when the eyelids are held open and the patient is told to close the eyes, then the principle of Motais, carefully used, may be applied

PARALYSIS OF INFERIOR OBLIQUE MUSCLE ALONE

Isolated paralysis of the inferior oblique muscle is rather uncommon. It may occur with or without ptosis

Paralysis of Inferior Oblique Muscle Without Ptosis—An illustrative case follows

CASE 1—In a white girl 9 years of age it had been noted that the left eye was "cast up." Central vision was 20/20 in each eye. She preferred to fix with the right eye. The palpebral fissures were equal. Left hypertropia of about 10 degrees of arc was evident. The excursion and monocular uncover tests disclosed weakness of the right inferior oblique with overaction of the left superior rectus muscle. In gazing up and to the right the eyes were practically level, whereas in gazing up and to the left there was at least 20 degrees of arc of left hypertropia. The inferior rectus and superior oblique muscles appeared normal. The child was able to fuse images in the lower fields. It was reasoned that for correction of this "casting up" it would be unwise to resect or advance the paretic right inferior oblique muscle, as the effect of the fixation with the paretic eye would still remain. It was judged best to do a recession of the left superior rectus. The result was excellent. There was no ptosis after the operation of

recession on this rectus, in the performance of which particular care was taken to free the normal connections between the muscle and the fascias, particularly of the overlying levator

Paralysis of Right Inferior Oblique Muscle with Real Ptosis—An illustrative case follows

CASE 2—A white girl aged 16 years had a history of forceps delivery with injury of the tissues of both orbits. The left eye was amblyopic, probably due to retinal hemorrhage at birth. Corrected vision was 20/30 in the right eye and 20/100 in the left eye. She carried her head level, raising her eyebrows and eyelids by means of her frontalis muscle. When the brows were held down, there was disclosed complete ptosis on the right side and partial ptosis on the left side. When the eyelids were held open and the patient was instructed to close her eyes, the eyes rolled up well and diverged. Evidently, she had a good right superior rectus muscle. Excursions and monocular uncover tests showed paralysis of the right inferior oblique muscle. She fixed with the paretic right eye, but there was practically no left hypertropia. Because there was no right hypotropia, or lowered level, of the right eye and because she had a good right superior rectus, it was decided to do a modified Mota's operation on the right eye. There was a definite indication for this because, first, there was evidence of complete paralysis of the levator muscle and the palpebral fissure was actually narrower on elevation than on depression of the eye, second, the superior rectus was active, and, third, any operation employing the frontalis muscle would result in continuation of the facial expression, which the patient disliked. In the correction of ptosis the use of the resection and advancement of the levator muscle or the Mota's principle is, if feasible, to be preferred to the use of the frontalis muscle. The modified Mota's procedure gave a satisfactory result in this case.

MULTIPLE PARALYSES OF ELEVATOR MUSCLES

There have come to my attention unusual cases which illustrate, each in a different way, the surgical problems of some of the more uncommon or complicated conditions of paralysis of ocular elevation. In all but 1 of them there have been hypotropia and real ptosis or pseudoptosis.

The conditions which will be discussed are (1) unilateral paralysis of the superior rectus and inferior oblique muscles with real ptosis and pseudoptosis, (2) bilateral paralysis of the superior rectus and inferior oblique muscles with pseudoptosis, (3) bilateral replacement of the superior rectus muscles by fibrous tissue with unilateral real ptosis, (4) unilateral complete paralysis of the third nerve with real ptosis; (5) unilateral paralysis of the third nerve with paradoxical ptosis, (6) bilateral complete external ophthalmoplegia with bilateral ptosis. I have observed also 3 cases of manifest cicatrix formation with various combinations of orbital atrophy, enophthalmos, strabismus fixus and ptosis and several cases of thyrotoxicosis with paralysis of elevation and ptosis but shall not describe them here. The phenomena of Marcus Gunn also will not be discussed. The causes of the other conditions included lesions in the supranuclear, nuclear and peripheral portions of

the oculomotor nerves and local orbital birth trauma with and without forceps delivery

UNILATERAL PARALYSIS OF SUPERIOR RECTUS AND INTERIOR OBLIQUE MUSCLES WITH COMPLETE REAL PTOSIS

CASE 3—A white girl aged 16 years was seen in 1936 with real ptosis. She had had a flat, expressionless, completely closed right upper eyelid since birth. There was no sign of a crease or fold indicative of the attachment of the levator muscle to the skin of the lid or of any activity of the levator. She was unable to open the eye even when the fellow eye was occluded. There was no evidence of the jaw-winking phenomenon. When the lid was lifted with the finger, the globe was found in a position of hypotropia of 20 to 30 degrees of arc. The eye was amblyopic, with vision of less than 20/200. The head was carried erect through the influence of the normal (left) eye and eyelids, and no effort was made to throw the head back, wrinkle the forehead, elevate the brow or in any other way try to use the right eye alone or with the left eye. There was no diplopia. The other extrinsic ocular muscles apparently were functioning. The attempt to improve matters therefore was on a purely cosmetic basis. The first effort was directed to raising the globe to a level with the primary position of the left eye. The procedure of resection and advancement of the atrophic remnants of the superior rectus and of the inferior oblique over the orbital margin² was resorted to. The result was as good as could be expected from the effect of tensing of atrophic muscle tissues which had practically no functioning fibers. It did not seem necessary to do a recession of the inferior rectus or the superior oblique, as these muscles appeared relaxed. After about three months an effort was made to correct the ptosis by suturing the superior rectus tissue to the upper border of the tarsus, the open method, through an incision in the skin, being preferred to the conjunctival exposure. Partial success was achieved, the opening of the lids being 5 mm, as compared with the 10 mm fissure of the normal (fellow) eye. I believe that now I should use a modified frontalis procedure for the final step in such a case, bringing down a thin band of fascia from beneath the mobile eyebrow to attach to the tarsus, and thus enable the patient to use the frontalis muscle better. Employment of the frontalis muscle is indicated in such a case, because there is no other way out of the difficult situation. Resection of the levator or tarsus or use of the Motais principle would fail. I should carefully avoid any injury or use of the orbicularis muscle, preserving the latter muscle intact, so that, aided by the relaxation of the frontalis muscle and the lowering of the brow, the patient may be able to close the eye and not suffer from lagophthalmos.

UNILATERAL PARALYSIS OF SUPERIOR RECTUS AND INTERIOR OBLIQUE MUSCLES WITH PSEUDOPTOSIS

CASE 4—A white man aged 42 had had a normal birth, but early in infancy his parents noticed that he could not open his right eye properly. He threw his head back, arched his eyebrows and corrugated his forehead in the effort to see with both eyes. At the age of 30 he had a Motais operation elsewhere for the correction of the ptosis. When I first saw him he had an evident paralysis of both the superior rectus and the inferior oblique muscle of the right eye and what was considered to be a real ptosis but was later recognized as a pseudoptosis on the same side. The left eye and eyelids were normal. He had 20/20

vision in the right eye with a correction of $+1.00$ D cyl, ax 100 and 20/20 in the left eye with a correction of -0.25 D sph $\subset +2.00$ D cyl, ax 140. Binocular single vision was obtained in the lower fields with the aid of the head-back position, but when an effort was made to bring the head nearer to the level position vertical diplopia was experienced and the right eye remained in a position of hypotropia of 30 degrees of arc. His paretic right eye was the dominant eye and was preferred for fixation with the head thrown back. On Aug 5, 1942 a 4 mm recession of the right inferior rectus was done, and the right inferior oblique was advanced over the orbital margin², at the same time an adhesion was effected between the right superior rectus muscle and the right upper tarsus. The cosmetic effect in the immediate postoperative period was satisfactory. The right hypotropia was reduced to 10 degrees of arc, and the lid was elevated so that the palpebral fissure was 7 mm. There was slight lagophthalmos, and the patient expressed himself as pleased with the result. He was again employable as a salesman. However, he soon experienced some annoyance with limitation of rotation of the right eye and with diplopia, and he acquired the habit of closing his right eye or of using an occluder. In retrospect, I should choose to be content with a lesser raising of the paretic right eye and should lower the left eye and use the principle of the vicarious action of the frontalis muscle through a brow fascia transplant rather than that of the lid-globe adhesion for the correction of the ptosis. Now, after a period of two years, the original conditions are returning in the stretching of the atrophic muscle fascias which were used to elevate the globe. There is developing again almost as much right hypotropia as there was before. A recession of the left inferior oblique and/or the left superior rectus muscle may be indicated to correct the secondary deviation of the left eye when he is fixing with the paretic right eye. This may bring the left eye down to the level of the right eye and improve the field of binocular single vision. It may also be necessary to do a recession of the right inferior rectus or the superior oblique muscle. Finally, the right lid-globe adhesion may be released and the frontalis muscle used for partial correction of the ptosis of the right lid through formation of a brow fascia transplant. The patient may be satisfied to retain some of the backward tilt of his head.

CASE 5—A white youth aged 16 had pronounced right hypotropia and pseudo-ptosis in the primary position. The right orbital area had been injured by high forceps at a difficult birth. He had always carried his head erect and level and with the right eye closed. He was able to open his right eye by sliding his jaw to the left, but not to the right. When he threw his head back, as when he was told to do so for the purpose of the test, the right upper eyelid opened and third degree binocular single vision was demonstrated in the lower fields. He has 20/20 vision in the right eye with a correction of -0.50 D sph -0.50 D cyl, ax 95 and 20/20 in the left eye without any lens. He evidently preferred to fix with the normal (left) eye and to keep his right eye closed. He was able to fix with the right eye when the left eye was occluded, and during such a test the right upper eyelid opened so that the palpebral fissure measured 8 mm. At times the right upper eyelid rose sharply and without control. There was a good fold and crease in the skin of the right upper eyelid, indicating the attachment of the right levator muscle (palpebrae superioris) and possibly a good levator muscle. As soon as the occluder was removed from the left eye or a shift forward was made from the position of head back, with binocular single vision in the lower fields, the right upper eyelid would snap down, shutting the right eye. The atypical jaw-winking phenomenon, which may be explained on the basis of a congenital

anomalous connection between the third and the motor fifth cranial nerve, was the only evidence that the pathologic process was not entirely local. Diplopia was feared and avoided by the patient and could not be mapped accurately. There was right hypotropia of at least 30 degrees of arc, with clinical evidence of complete paralysis of both the superior rectus and the inferior oblique muscle on the right side. Screen tests in the cardinal positions did not demonstrate conclusively that the other extrinsic muscles of the right eye were entirely normal. The attempt to demonstrate Bell's phenomenon failed. The right eye did not rise at all when the order was given to close the right eye while the upper eyelid was held up. The muscles of the left eye were apparently normal. On Nov 20, 1944, with the patient under ether anesthesia, the passive motion of the globe was tested and was found to be restricted, as though the superior rectus were partially replaced by fibrous tissue. The procedure of resection of the superior rectus was accomplished with difficulty because of the bleeding of the enlarged vessels and the thickening and fibrosis of the muscle. Particular care was taken to release the connections between the superior rectus and the levator muscle to prevent the development of real ptosis. The lack of plasticity of the muscle tissue was probably a sequela of the birth injury and did not offer a good prognosis for other than a limited field of useful binocular vision in the new elevated position. The right inferior oblique muscle was exposed through an appropriate cutaneous incision in the inferonasal orbital margin and was found to be thin, yellow and flaccid. Evidently it had not been injured but was in a condition of partial atrophy of nonuse. It was advanced over the orbital margin³ in the effort to enhance its action, although the outlook was not hopeful because of its atrophic condition and because of the partial fixation of the globe by the fibrosed superior rectus. Immediate postoperative observations showed no improvement in the position of the lid, but later he opened the eyelids easily to 5 mm. It had been hoped that the lid would open when the globe was elevated. When the upper eyelid was lifted manually, it was noted that elevation of the right eye had been effected to an overcorrection of 10 degrees in the primary position and of 15 degrees in the lower fields. Observations of diplopia were in agreement with this but could not be charted. If, as may be expected, the temporary overcorrection becomes less and the right globe comes down to the level of the left eye in the primary position, then the right upper eyelid may be lifted by using the frontalis muscle through formation of a brow fascia transplant, or by resection of the levator and tarsus. The patient cannot now lift his right upper eyelid by throwing his head back, but he can still open his right eye by grinding his jaw to the left. It cannot be expected that a limited field of binocular vision will be entirely satisfactory to the patient, particularly because of the right hypertropia and diplopia now present in the lower fields. He has learned to make use of his stereoscopic vision with his head level and nearer the primary position. He has learned to move his head to keep his eyes in range for fusion in certain acts of skill in a limited field. Certainly, he will prefer to close his right eye for any rapid appraisal of a situation or when in danger or when confronted by moving objects. Under such conditions, he will probably again resort to his experience and judge by parallax form, direction, speed and distance with his left eye alone. Further surgical treatment will depend on complete resolution of the tissues, after a proper length of time has elapsed. Another operation may well be in order for the further correction of the ptosis.

3 Wheeler, J. Advancement of the Superior Oblique and Inferior Oblique Ocular Muscles, in *Collected Papers of J. M. Wheeler*, New York, Columbia University Press, 1939, *Tr Am Ophth Soc* 32:237-244, 1934.

BILATERAL PARTIAL PARALYSIS OF SUPERIOR RECTUS AND
INFERIOR OBLIQUE MUSCLES WITH BILATERAL
PSEUDOPTOSIS

CASE 6—The condition of bilateral hypotropia with pseudoptosis was observed in a white youth aged 14 years. It had been present since birth and was attributed to injury by forceps at birth or by a fall on his head at 10 months of age. He had always had a habit of throwing his head back. He arched his eyebrows but did not corrugate his forehead. The palpebral fissures with the head back measured 8 mm on the right side and 7 mm on the left side. When the head was brought to the level position, the patient's eyes were cast down, and all efforts to elevate his eyes failed, vertical searching movements and irregular nystagmus becoming

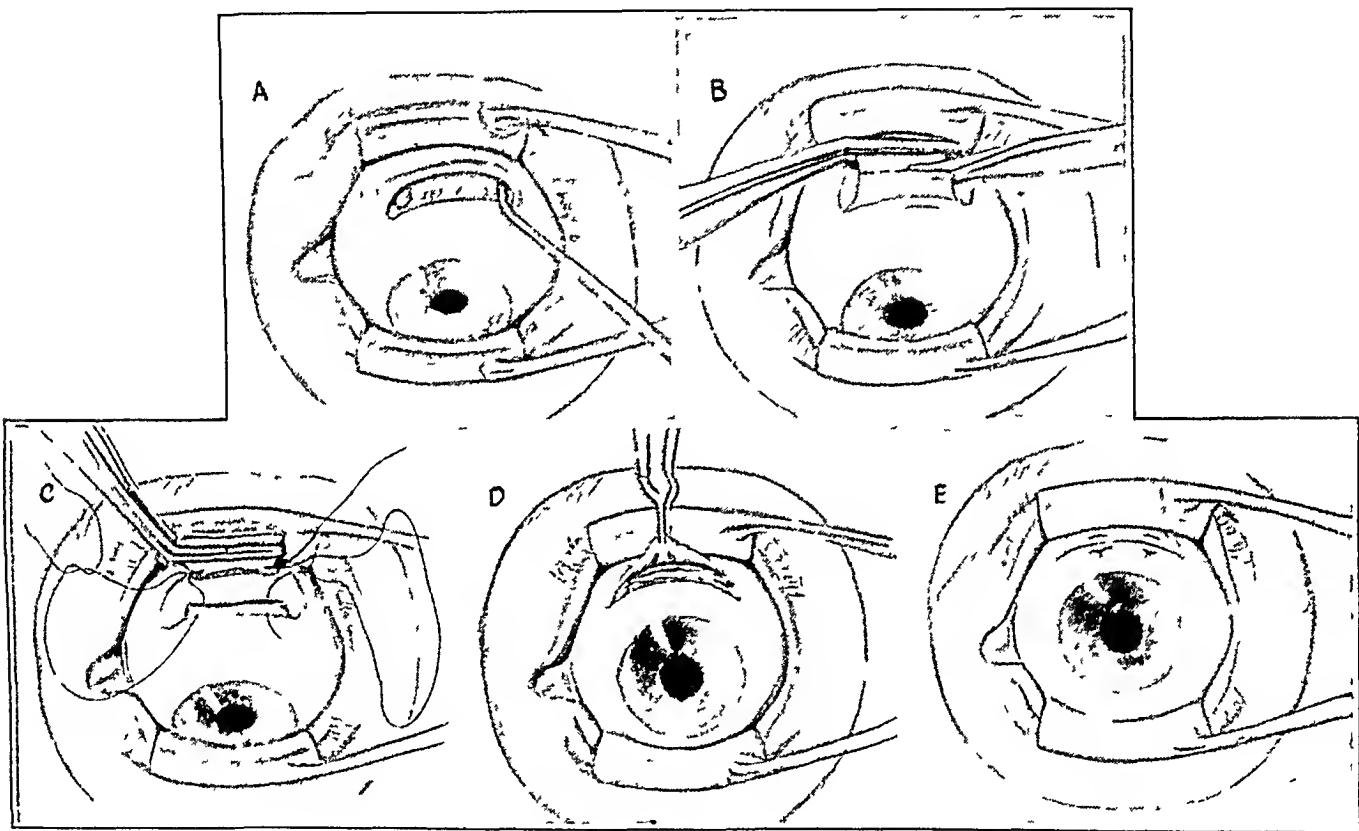


Fig 1—Resection and advancement of the superior rectus muscle (left eye illustrated)—A, exposure with the speculum and the eye looking down. The incision through the conjunctiva and Tenon's capsule is completed. A hook, with round handle, is placed under the superior rectus muscle from the temporal side. Tenon's capsule is separated and retracted, exposing the muscle.

B, the muscle freed from Tenon's capsule and its elevator connections. Multi-toothed forceps are placed on the superior rectus muscle 4 mm from the tendinous insertion. Scissors are shown severing the muscle just central to the forceps, leaving a 2 to 3 mm stump of muscle at the insertion.

C, insertion of white silk 00000 sutures on a small atraumatic needle. The suture is passed through the outer fourth of the muscle fibers to cinch the fibers and then through the insertion of the muscle just behind the muscle stump.

D, muscle forceps removed. The sutures advancing the muscle forward to the new position have been tied. The eye moves up toward the primary position.

E, closure of conjunctiva with two interrupted mattress sutures (plain 0000 surgical gut).

evident Diplopia was not experienced or demonstrated The eyelids did not rise, and the palpebral fissures measured 4 mm when the head was brought forward The eyes did not rise when the lids were held open and the patient was instructed to close his eyes Tilting the head forward gave greater evidence of the patient's inability to look upward or to raise his eyes when attempting to look up The patient could look to the right and to the left when the head was thrown back in his

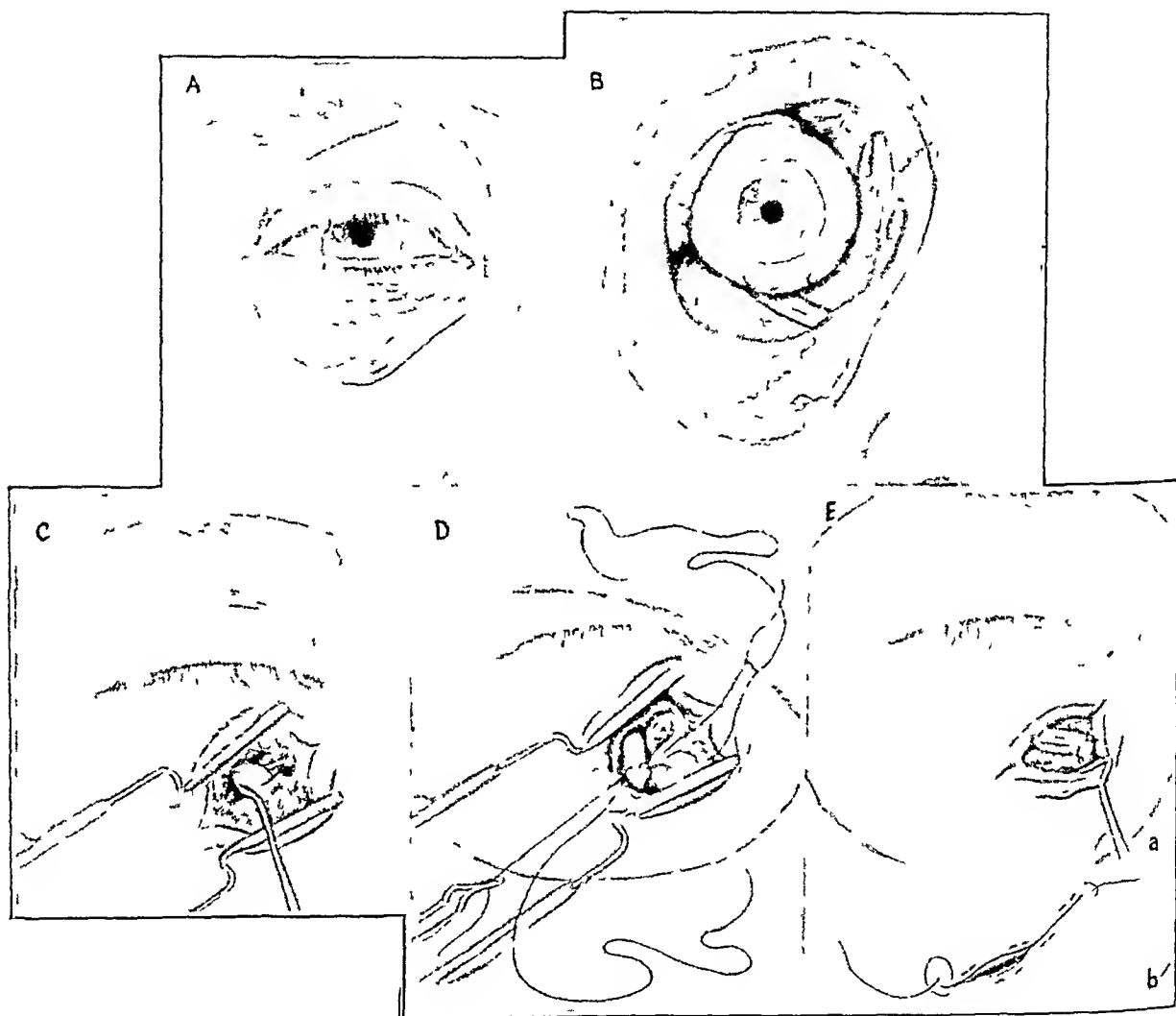


Fig 2—Advancement of the inferior oblique muscle over the orbital margin (right eye illustrated)—*A*, phantom drawing, showing curvilinear cutaneous incision over the inferior nasal orbital margin and location of the inferior oblique muscle

B, drawing showing surgical anatomic relations of the inferior oblique muscle

C, surgical dissection, exposing periosteum of the nasal bone and showing the inferior oblique muscle on a muscle hook at its origin on the orbital margin A multitoothed speculum is used

D, two white silk 0000 ten day chromic surgical gut sutures on stout, small, fully curved needles, used to cinch muscle fibers and then inserted into the periosteum

E, advancement of the inferior oblique muscle over the orbital margin Sutures have been tied The inset shows the subcuticular 00000 black suture for closure of the cutaneous incision

usual, or customary, position There was a good crease or line and fold in each upper eyelid as evidence of attachment of the levator muscle to the skin and of activity of the levator muscle It was surmised that the lids were down because the eyes remained down in the position of hypotropia and because he had bilateral paralysis of ocular elevation Central vision was 20/30 in the right eye with a correction of -6.00 D sph $\ominus -1.75$ D cyl, ax 20 and 20/30 in the left eye with a correction of -4.00 D sph $\ominus -2.00$ D cyl, ax 180 He had third degree binocular single vision with his head back The diagnosis of paralysis of elevation of both the superior rectus and the inferior oblique muscle of each eye with pseudoptosis was made There was no evidence of fixation of the globe or of fibrous replacement of muscle tissue On Nov 18, 1943, with the patient under ether anesthesia, the elevator muscles of the left eye were exposed and found to look fairly healthy Recession and advancement of the left superior rectus muscle and advancement of the left inferior oblique muscle over the orbital margin were performed Seven days after the operation on the left eye, when Dr James White was called in consultation to see the patient, there was a difference of 25 to 30 degrees of arc in the vertical positions of the eyes, the eye on the side of operation then being that much higher than the other eye There was a great temptation to vary the procedure for the second eye and to do a resection of the inferior oblique muscle at or near its insertion, but not knowing the comparative values of resection at the insertion of the inferior oblique muscle and of advancement at its origin, I decided to repeat as nearly as possible the technic used for the first eye This was done on November 23, and the final result was gratifying to the patient and to his parents He was rid of his psychologic handicap, he was able to hold his head and eyes level, and the right palpebral fissure was 9 mm and the left 8 mm when the eyes were in this position It is worthy of note that resection of the superior rectus muscles in this case did not produce a real ptosis His downward gaze was unimpaired, but he could not look up higher than the primary position with his head held level This was expected to be less of a handicap as he grew taller Happily, the eyes were level, and test with the Maddox rod and with prisms showed less than 1 prism diopter of left hyperphoria He had good fusional reserve and was able to maintain third degree stereoscopic vision in and below the level position of the head He still had vertical nystagmus when he attempted to look above the primary position with his head held level

BILATERAL REPLACEMENT OF SUPERIOR RECTUS MUSCLE BY FIBROUS TISSUE WITH UNILATERAL REAL PTOSIS

The congenital anomalous fibrosis of extrinsic ocular muscle tissue, such as that of the external rectus muscle, is a familiar picture The finding, however, of definite fibrous replacement of the tissue of the superior rectus muscle at an operation for reconstruction in a case of ptosis is unusual In fact, I have not found a case of it reported in the literature on ptosis

CASE 7—The patient was a shy, though mentally normal, white girl of 3 years who since birth had been unable to look up well with either eye and had been unable to open her right eye Examination was difficult because of lack of cooperation Excursion cover tests attempted in the six cardinal positions revealed a definite limitation of rotation of the eyes, movement of the head being favored There were 10 or more degrees of bilateral hypotropia when the head was held level.

She either did not attempt to look upward or threw her head well back. The test for Bell's phenomenon gave negative results. Nevertheless, because the palpebral fissure was narrower in upward than in downward gaze, plans were made and carried out for doing a modified Mota's operation. This was accomplished with difficulty. Tests of passive motility of the globe made with a muscle hook and then with forceps with the use of anesthesia gave the impression of partial fixation of the globe. The tissues of the lids were fibrosed, hard and difficult to separate in the usual planes of dissection. The exposure of the right superior rectus muscle revealed definite fibrosis and fixation of the muscle. It was about 9 mm wide and 1 mm thick. The union of the transplanted central third of the muscle tissue with the anterior face of the tarsus was accomplished with difficulty because of the fixation and lack of plastic yielding of the tongue of muscle. Two weeks after operation there were evident a moderate amount of entropion and a downward displacement of the eyelashes, but no dystriachiasis. It is now nearly one year since the operation, and there still remain the hypotropia and the inability to look up with either eye, a definite amount of ptosis of the right lid but practically no discomfort. The cornea remains intact. There is no photophobia or lacrimation. The child is able to close the eye voluntarily by action of the orbicularis muscle of both upper and lower eyelids. The eye remains open 2 mm during sleep. In the usual case of ptosis, with intact superior rectus muscle, there is normal plasticity or yielding of the muscle and lid tissues. The care of this little patient is being carried on conservatively, the question being debated whether one should undo the lid-globe adhesion and perform the brow fascia-tarsus operation and be satisfied with the hypotropia or whether a moderate recession of one or both inferior rectus muscles might be done in an effort to raise the plane of the globes so that she may hold her head level, with the eyes nearer the level or primary, position.

In retrospect, now, I can recall 1 other case of my own in which two previous operations had been done elsewhere for the correction of ptosis, one procedure evidently being a Mota's and the other a frontalis operation. Entropion had developed, so that the lashes nearly touched the cornea. The patient was satisfied to have the eye open and to be able to close it with the orbicularis. No erosion of the cornea had developed, and the patient had carried on for over six years and had not wished to have the transplant released. In 2 other cases I was consulted because of the development of this undesirable postoperative entropion, and I did not consider it due simply to an overcorrection or a faulty placement of sutures. It obviously is evidence of the existence of fibrosed or unyielding, nonplastic tissue of the superior rectus muscle, which when encountered should be reason for being satisfied with a partial or an imperfect correction of the ptosis, one which will not produce entropion, dystriachiasis or lagophthalmos of any degree or danger. It might be better to correct the hypotropia if this is possible and then use the frontalis muscle for partial correction of the ptosis. Such experiences indicate the advisability of not using the Mota's procedure if there is any fibrosis of the superior rectus muscle or if there is hypotropia. In case of the latter, it may be well to do a recession of the

inferior rectus and/or the superior oblique muscle to help in correcting the hypotropia

UNILATERAL PARALYSIS OF THE THIRD NERVE

Patients with this condition may exhibit various phenomena, depending on which portions of the nucleus or which fibers of the third nerve are affected and which fibers have regenerated. There may be partial or complete paralysis of any or all of the muscles supplied by the oculomotor nerve. There may be constant or paradoxical ptosis. In the latter condition the upper lid may rise incoordinately when the patient attempts to move the eyes. The desire of such a patient for cosmetic relief from the blemish and the personality difficulty consequent on such a condition may lead the surgeon to try to help in some way. The poor prognosis for satisfaction, however, should generally bring the decision that no operation is best.

CASE 7—In a girl aged 16 years complete paralysis of the right third nerve had developed in early childhood as a complication of an undiagnosed febrile illness. There were complete constant ptosis on the right side, with a smooth, flaccid upper eyelid, exophthalmos of the right eye, the forward projection being 5 mm. more than that of the fellow eye, dilatation to 6 mm. of the pupil and absence of reaction to direct stimulation with light, limitation of central vision to perception of hand movements, myopia of about 6 D. as measured objectively, and a position of exotropia and hypotropia. The eye was not completely immobile, as it could be moved laterally and exhibit intorsion as evidence of activity of the external rectus and of the superior oblique muscle.

CASE 8—A woman aged 20, a clinic patient, came for relief of ptosis of the right lid, which exhibited a peculiar behavior. The condition was of unknown origin. The dropping of the right upper eyelid was complete when the left eye was in the primary position. The left eye appeared normal. When the right upper eyelid was lifted, it exposed the right eye in pronounced hypotropia. When the upper eyelids were held open and the patient was told to close her eyes, the right globe did not rise, whereas the left one did. She was able to look to the right with the aid of the right external rectus muscle and the right upper eyelid remained motionless, but when she was told to look to the left there was a marked spasmodic elevation of the right upper eyelid. When she tried to look up, the right upper lid snapped up, but the globe remained well down, while in the effort to look down there was a slight degree of elevation of the eyelids.

One may suppose that secondary deviation, anomalous innervation or erroneous regeneration of nerve fibers accounts for the incoordinate behavior of the eyelid. Bielschowsky⁴ used the last hypothesis to explain the phenomenon in a case quite similar to mine. He rejected Fuchs's explanation of this pseudo-Graefe phenomenon, namely, that when the nucleus of the third cranial nerve is diseased or injured the

⁴ Bielschowsky, A. Lectures on Motor Anomalies, Hanover, N. H., Dartmouth College Publications, 1943, pp. 83-86.

nervous stimulation sent to a part of the nucleus extends over to neighboring parts, so that unintended as well as intended movements are obtained. His own hypothesis was that in the course of regeneration some of the fibers which proceed from the central part of the trunk of the third nerve do not find their original sheaths in the peripheral parts of the nerve but, going astray, arrive at muscles to which they do not belong, thus accounting for the bizarre reactions and movements. In any event, the poor prognosis for achieving anything approaching motility alone or in unison with the fellow eye in either of these cases and for coordinating the discordant movements of the upper eyelid in the second case will probably make the surgeon decide against operation unless the fellow eye is amblyopic and the patient needs the paretic eye for its better vision. If the condition is bilateral, the procedure to be described in the next case may be used. A procedure which has been thought of, but never employed, is that of detachment of the intact superior oblique muscle from its pulley and its attachment to the upper eyelid.

BILATERAL COMPLETE EXTERNAL OPHTHALMOPLÉGIA WITH BILATERAL COMPLETE REAL PTOSIS

CASE 9.—This condition in a white man aged 45 was part of a picture of progressive degeneration of the cranial motor nerves of undetermined origin. The use of neostigmine produced no change. The onset was at the age of about 36. His face had become masklike and expressionless. He had 20/30 vision in the right eye and 20/50 in the left eye with correction. There was complete absence of binocular single vision and diplopia when both upper lids were lifted. He had the average power of accommodation in his right eye for his age group. He was able to make his way about the city by himself in the characteristic way of holding up the right upper eyelid at its outer corner with his right thumb. He tired of this and requested that his right eye be opened to a degree equivalent to which he held it with his thumb. This did not seem to be much to ask, but there was the problem of possible lagophthalmos, such as was present in his left eye after an unsuccessful surgical attempt to raise the left upper eyelid. The pupil of the left eye was higher in its immobile position than that of the right eye, and cicatrization of the left upper eyelid following the operation had interfered with the closure action of the left orbicularis, even so the left pupil was not exposed. Tests were made to try to duplicate the elevating action of the patient's thumb on his right upper eyelid. It was observed that he placed his thumb at the outer third of the eyebrow and assisted it somewhat by arching his right brow and corrugating his forehead. The upper branch of the seventh, or facial, nerve was evidently nearly or completely intact. Tests for sensitivity and for the rate of lacrimal secretion gave normal results. The test with a strip of adhesive holding the right upper eyelid open was unsatisfactory, redness and watering of the right eye developing probably because of the interference with the orbicularis. A silk suture was tried, passing it from the skin of the outer third of the upper eyelid from just beneath the brow up and over the brow. This test proved satisfactory, and the patient was able to go about and had approximately the same

lid-elevating effect with the aid of the suture and his frontalis muscle as with his thumb. He was able to relax his brow, to contract his orbicularis and to close his eye. He had no redness, watering or other sign of lagophthalmos, either during his waking or his sleeping hours, for the seventy-two hours of the suture test. Operation, with use of local anesthesia, was decided on. Procaine block of the supraorbital and infraorbital nerves and some infiltration were used. Then a 25 mm incision was made in the skin about 2 mm above the tarsus of the right upper eyelid, and a 3 mm strip of redundant skin was excised. The orbicularis fibers were separated, care being taken not to injure them. The Reese⁵ modification of the Machek operation was decided against because it employs orbicularis fibers, which should be preserved for closure of the eye. Deep, nonyielding, cicatrizing sutures were not used because they would in the end produce lagophthalmos. The burial of skin flaps uniting the lid of the brow might produce an undesirable exfoliative condition in cystic pockets. The fascia of the levator, which it was thought I might employ to join the upper eyelid to the brow, was so atrophic that it was useless. I did not wish to introduce foreign or grafted tissue, and I was left with only one tissue, that of the fascia from beneath the brow. This fascia is in loose union with the fascia of the eyelid normally and is the fascia through which the patient with ptosis usually lifts his eyelid when he arches his brows and corrugates his forehead. Dissection upward in the plane of this fascia revealed that a suitable flap, about 1 mm thick and 10 mm. wide, attached to the brow could be fashioned from beneath the brow. Repeated tests were made with the patient's cooperation to show first the power of elevation of the brow, and then, with the properly adjusted attachment of the fascia to the anterior face of the tarsus, the desired degree of elevation was achieved, the fissures being opened to 6 mm and a small portion of the pupil exposed, which I was careful to observe was of the same size as it ordinarily was before the operation. The result has been very satisfactory to the patient. He is able to do as well now in utilizing the elevating power of his frontalis through his brow as he was previously with the aid of his thumb. There is no lagophthalmos of the right eye.

SUMMARY AND CONCLUSIONS

The conditions of paralysis of ocular elevation with and without ptosis are described, and various cases illustrating the different types according to the muscles paralyzed are reported. The purpose of the paper is to bring out the indication for, the application and the technic of surgical procedures which may be useful in correcting the hypotropia of the paretic eye or the hypertropia of the sound eye which develops when the paretic eye prefers to fix and, finally, in correcting the ptosis. The differentiation is made between real ptosis and pseudoptosis.

The following conditions are evaluated from the surgical standpoint (1) paralysis of the superior rectus muscle alone, (2) paralysis of the inferior oblique muscle alone, (3) unilateral paralysis of the superior rectus and inferior oblique muscles, (4) bilateral paralysis of both

⁵ Reese R. E. An Operation for Blepharoptosis with the Formation of a Fold in the Lid. *Arch. Ophth.* 53:26-30, 1924.

superior rectus and inferior oblique muscles and (5) bilateral complete external ophthalmoplegia. In all these conditions the association of ptosis is considered. The surgical correction which is possible, the procedures which are feasible and the methods used in applying the principles of reconstructive surgery to these conditions and the actual results obtained in the cases reported are given.

In the case of real ptosis without paralysis of elevation the principles of resection and advancement of the levator and smooth muscle of the upper eyelid should be applied when the ptosis is partial, whereas the indication is for the Motaïs principle when the ptosis is real and complete. The continuation and enhancement of the patients's use of the frontalis muscle should be reserved for those cases in which the application of the levator muscle or the Motaïs principle is not feasible.

In the case of paralysis of the superior rectus with overaction of the inferior oblique of the fellow eye, the indication is for myotomy, myectomy or recession of the latter muscle. If there is real ptosis with paralysis of the superior rectus, but with an intact inferior oblique and no hypotropia of the same side, then the Motaïs principle may be employed for the correction of the ptosis.

In a case of paralysis of the inferior oblique alone with overaction of the superior rectus of the fellow eye, recession of the latter was successfully employed. In another case of paralysis of the inferior oblique with ptosis on the same side, but with a good superior rectus, the Motaïs principle was applied with satisfaction.

Multiple paralyzes of elevator muscles present unusual problems.

In a case of unilateral paralysis of both superior rectus and inferior oblique muscles and with real ptosis, the hypotropia was corrected by resection of the superior rectus and advancement of the inferior oblique muscle over the orbital margin. Use of the Motaïs principle was contraindicated, whereas the frontalis operation appears to offer some hope for correction of the ptosis.

In cases of unilateral hypotropia with pseudoptosis, the former was corrected first to learn the subsequent behavior of the eyelid before deciding whether or not to use the frontalis principle or the resection of the levator and tarsus for correction of any residual ptosis.

In a case of bilateral hypotropia with partial paralysis of the superior rectus and inferior oblique muscles and pseudoptosis, resection of the superior rectus and advancement of the inferior oblique muscles correct both the hypotropia and the pseudoptosis. It is noteworthy that resection of the superior rectus muscle with careful freeing of connections between this muscle and the levator produced no real ptosis.

In cases of complete oculomotor nerve paralysis with real and with paradoxical ptosis it is difficult, if not impossible, to achieve any satis-

faction when the paralysis is unilateral. If the condition is bilateral, then the same procedure as that previously described may be employed.

A case of fibrous replacement of the superior rectus muscle is reported. In such conditions, when detected, the indications are for use of the frontalis muscle rather than the Motais principle, and if there is hypotropia the recession of the inferior rectus or the superior oblique muscle may be indicated.

In a case of bilateral complete external ophthalmoplegia with complete real ptosis, I employed the frontalis muscle principle, resecting and advancing the fascia which normally forms a loose connection between the brow and the lid. A partial, though satisfactory, opening of the palpebral fissure without lagophthalmos resulted.

780 Park Avenue

DISCUSSION

DR. JAMES W. WHITE, New York: I have been privileged to see 3 of Dr. Kirby's patients. The most interesting was the one I saw after he had resected the superior rectus and had resected and advanced the inferior oblique over the orbital margin. I suggested that he might splice the inferior oblique near the insertion. Since he was sure he could duplicate the operation on the first eye, he chose this method, and he did duplicate it exactly. The conditions in the two eyes were identical, and the results were also identical.

My lantern slides will show all I wish to say, and they touch on some parts of Dr. Kirby's paper.

CASE 1—The child had paralysis of both elevator muscles of the right eye, he held his head back to get binocular single vision in the lower fields. With the head held back, the field of binocular single vision was one-third the way above the horizontal line. The superior rectus was only slightly paretic, but the inferior oblique was much weaker. He had no ptosis, however. I resected the superior rectus muscle and followed with the Wheeler procedure on the inferior oblique muscle. He held his head perfectly straight and had binocular single vision up to a point one-third the way above the horizontal line.

CASE 2—The patient had paralysis of both elevator muscles of the left eye and fixed with the nonparetic eye. Both paretic elevators of the affected eye were shortened. This patient had hypotropia and pronounced real ptosis. After the eye was raised, the operation for ptosis could be safely done.

CASE 3—The patient had paralysis of both elevator muscles of the left eye, fixing with the paretic eye. This lad had 20/20 vision in the paretic eye and 20/200 in the nonparetic eye. He had some ptosis and a pronounced secondary deviation of the superior rectus and the inferior oblique muscle of the nonparetic eye. When he looked up, the cornea was almost hidden by the upper lid, both in the eyes up and right and in the eyes up and left position. The procedure which gives the best results in such cases is a tenotomy or recession of both the elevator muscles that are overacting. I did a nearly complete tenotomy of the superior rectus muscle and a complete tenotomy of the inferior oblique muscle through the skin. I should now do a complete tenotomy at the insertion, which would give about the same result as a complete tenotomy or a myectomy at the origin.

The palpebral fissure of the paretic eye is not normal, and the patient still has the ptosis. Operation for its correction has not been performed. He now has moderately good elevation of the eye operated on. The paretic eye is a little above the horizontal line. It is for the operator to choose what to do for the ptosis.

CASE 4—This patient has bilateral paralysis of the superior rectus muscles, vision is 20/20 in the right eye and 20/50 in the left eye. With the eyes looking up and right, there is a well marked upshoot of the left eye, with an attempt to obtain fusion with the eyes down. He had binocular single vision in the lower fields. A satisfactory result was obtained, with tenotomy of both inferior oblique muscles.

CASE 5—Pseudoptosis of the retraction syndrome is a type of ptosis I do not know anything about. Unfortunately, in cases of this condition, one cannot conscientiously dissect out the orbit and find out why the retraction syndrome acts as it does. The boy in this case does not show the retraction of the globe as well as I wish he did. There are narrowing of the palpebral fissure, increased in adduction, and complete failure of abduction. The retraction syndrome is often bilateral, with a limited outward rotation of each eye. I used to hesitate to operate in cases of this syndrome, but I think I have obtained some of my most satisfactory results in such cases. So far as the ptosis is concerned, I think the results are unsatisfactory from one point, which I shall discuss later.

CASE 6—This patient, a pretty child, had a retraction syndrome. The palpebral fissure is reported as looking much better. I resected the fibrous rectus externus and did a recession of the fibrous rectus internus. To do that, one must be careful that the rectus internus can afford recession or tenotomy, lest the near point of convergence be made more remote, in which case a bad matter has been made worse. Such a result is not very likely since the internal rectus muscle will stand a tenotomy of greater extent in cases of this syndrome than in a case of strabismus fixus. What appears to be ptosis in the eyes-front position, increasing in adduction, usually changes to more or less pronounced widening of the palpebral fissure in abduction. It is often possible to bring the field of binocular single vision a little farther out by resecting and doing a recession of the fibrous muscle, being careful not to increase the retraction of the globe, which is present in practically all cases. The result is usually a cosmetic improvement.

CASE 7—A child of 4 years had such a disfiguring squint that I felt something had to be done. I did a recession of both internal muscles. They were fibrous, a condition characteristic of the retraction syndrome. The eyes came out a little from the inner canthus. They still could not move up or down or abduct. I turned the case over to Dr. Harold W. Brown. Both superior rectus muscles, as well as both inferior rectus muscles, were fibrous. The child still cannot abduct the eye beyond the midpoint. She still has ptosis and wears a crutch glass. I do not know whether I missed a point in diagnosis in this case. I suspect that I did, and I am going to correct it as soon as I can.

A patient I saw about a week ago had a condition much worse than this, and I knew it was out of my domain. I sent her to Dr. George Blakeslee for a neurologic report. He got no electrical reaction over the distribution of the facial nerve except slight response about the alae of the nose and the corners of the mouth. The patient had been troubled with slobbering, and she could not masticate her food properly. As a baby, she had always lain on her face. Dr. Blakeslee's report was that of complete abiotrophy of the facial nerve.

DR RUDOLPH AEBLI, New York The ptosis associated with imbalances of the vertical ocular muscles is a complex one and difficult to handle. In general, it must be remembered that the position of the upper lid is normally midway between the limbus and the pupillary margin of the iris, and the position of the lower lid is just at the limbus. The lid follows the hypotropic eye downward, and hence there is a pseudoptosis. The surgical principle involved is to place the two eyes on the same horizontal level and subsequently to correct whatever residual ptosis there is. In the presence of a weak or fibrotic superior rectus muscle, I do not favor the Motais procedure of correcting any remaining true ptosis but prefer an operation of the third group, namely, the production of more intimate adhesions between the lid and the occipitofrontalis muscle.

In some cases the patient fixes with the sound eye, and then the fellow eye is lower, with marked ptosis. In these cases the operation of choice is to raise the lower eye by resecting and advancing the superior rectus and tucking the inferior oblique muscle. In other cases the patient fixes with the paretic eye, and then the sound eye is higher, with sclera showing at the lower limbus. The cosmetic deformity is usually more pronounced under these circumstances. In cases of this type the operation of choice is to do a recession of both the superior rectus and the inferior oblique of the sound eye. In some cases the eyes alternate, when the patient is fixing with the sound eye the paretic eye is lower, and when he is fixing with the paretic eye the sound eye is higher. In cases of this type the operation should be divided between the two eyes. The lower eye is raised by resection of the superior rectus muscle, and the higher one is lowered by recession of the inferior oblique muscle. Dr. White has called attention to the importance of the fixating eye, if the principles which he emphasized are followed, results will be less likely to be disappointing.

In closing, I should like to show a few slides of congenital ptosis illustrating the principles I have enumerated and a few slides of acquired forms of both pseudoptosis and true ptosis associated with imbalances of the vertically acting muscles.

DR DANIEL KIRBY, New York I have learned a great deal from Dr. White concerning the pitfalls of erroneous diagnosis, I think that the diagnosis is the most important consideration before a surgical measure is employed.

PARALYSIS OF CONVERGENCE WITH BILATERAL RING SCOTOMA FOLLOWING INJURY TO OCCIPITAL REGION

A FEIGENBAUM, M D

AND

W KORNBLUETH, M D

JERUSALEM, PALESTINE

REPORT OF A CASE

S. A., a Palestinian Jew 22 years of age, presented himself for the first time in the outpatient department of the Hadassah University Hospital on Nov 14, 1944, complaining of diplopia for near and distant objects, headaches, sensation of pressure in the head, frequent attacks of dizziness, loss of equilibrium while bending forward and weakened memory

History—There was nothing of importance in his family history Except for scarlet fever, angina and pneumonia in childhood and, at the age of 20, malaria and a slight injury to his left arm caused by bomb splinters while he was serving with the armed forces, he had had no disease which could be connected with his present condition At the age of 19, in 1941, he joined the British army as a sapper In October 1942, while working in a well at a depth of 40 meters, he was struck on the head by a large stone which fell from above As far as he knew, he lost consciousness instantly, and on regaining it after some hours he found himself at a military hospital He was later told by his fellow workers that after having been injured in the well he managed to climb up and collapsed at the moment he came to the surface

His diplopia dated from the first day of his admission to the hospital and had not changed since in degree or quality At various periods during his stay in the hospital he lost consciousness for several minutes On one occasion, when he recovered his senses the fingers of both hands were still in a convulsive state ("obstetrician's posture"), and for several minutes he was unable to move them freely After having spent about eight months in the hospital, he was eventually discharged from the army because of total incapacity, in September 1943

General Physical Examination—Examination revealed in the young patient, who exhibited a fine physique, no special changes except three round depressions which could be felt in or near the occipital region At a distance of 8 cm above the external occipital protuberance in the median line there was one round depression, 1.25 cm in diameter, and a second one, of the same size, lay 2 cm to the right of the first depression A third depression, the largest one (2 cm in diameter), was situated 13 cm from the external occipital protuberance (measured along the surface of the head) and 3 cm to the right of the median line, or about 3 cm behind the vertex Roentgenograms (fig 1A and B) showed a depressed fracture of the right parietal bone, which corresponded with the last-

From the Ophthalmological Department of the Hadassah University Hospital

mentioned depression and which most probably was the original injury. The two other depressions may have been due to some surgical intervention (trephining?) during the patient's stay at the military hospital, of which no report could be obtained.

Neurologic Examination—No disturbance was evident in motility, superficial or deep sensibility, equilibrium or reflexes. There were no pathologic reflexes. Nothing abnormal in the psychic behavior of the patient was noted.

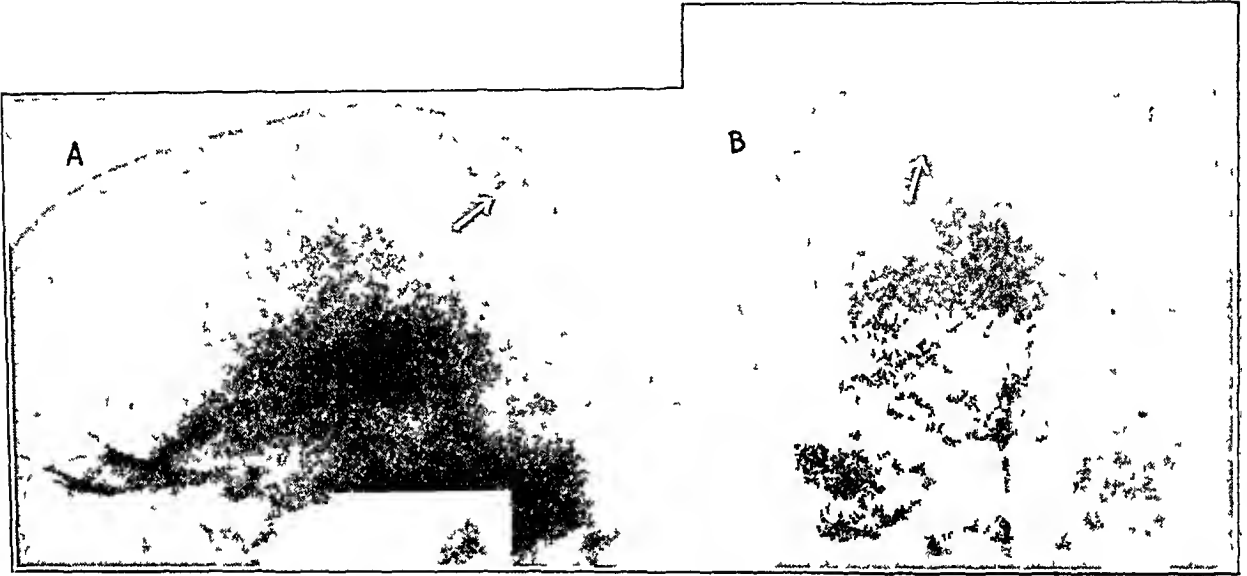


Fig 1—Roentgenograms of the skull. (A) lateral view, (B) posteroanterior view. The arrows point to the depressed fracture.

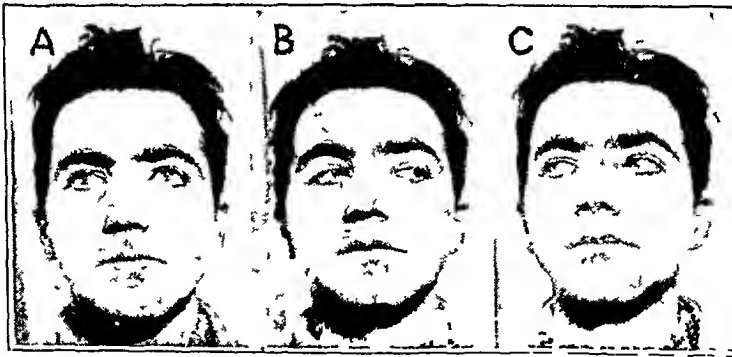


Fig 2—A, eyes looking straight forward, B and C, lateral associated movements.

Ocular Examination—The palpebral fissures were of equal width. Slight divergence (10 degrees on the perimeter) of the right eye (fig 2 A) was noted. Ocular movements were free in all directions. There was no disturbance in function of either internal rectus muscle in conjugate lateral movements (fig 2 B and C), but convergence of the eyeballs could in no way be elicited. At the most some very slight, jerky, nystagmoid movements resulted from such futile attempts at convergence.

There was crossed diplopia, with practically no difference in level of the eyes. Separation of the images was greater while the patient was looking straight forward than when he was looking sideways, in the two lateral positions the distance remained the same. The separation decreased when vision was directed downward, and it was at its maximum when the patient was looking upward (fig 3).

The examination for diplopia was repeated several times. The exact determination of the degree of diplopia, however, presented some difficulty, not usually met in cases of simple muscular palsies. The patient frequently asserted that the separation of the images was labile, as though they were oscillating, so that the degree of separation was constantly, though slightly, changing. This may be attributed to the futile attempts at convergence previously mentioned. A second difficulty encountered was the frequent alternation of the fixing eye, with a corresponding shift in the crossed diplopia from right to left and vice versa.

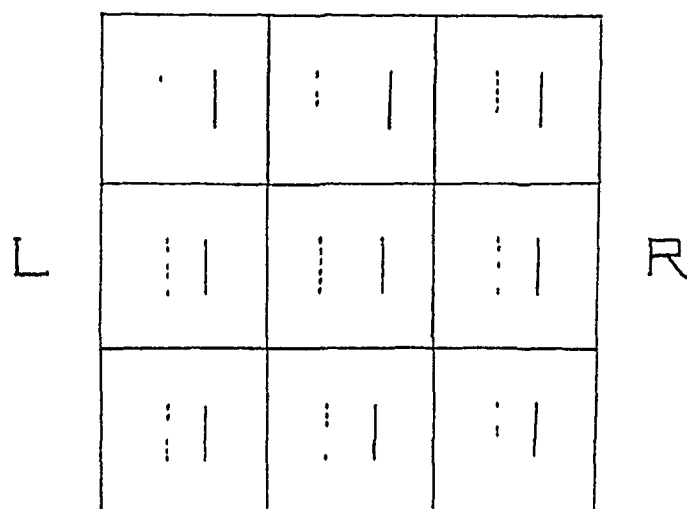


Fig 3—A chart (one test), showing crossed diplopia. Separation of images was greater when the patient was looking straight forward than when he was looking sideways. The separation was greatest on his looking up and least on his looking down.

The prism test (base outward) with gradual increase in power did not produce any fusional movements, the distance of double images simply increased for near objects.

Externally the eyes did not present anything abnormal. The media were clear and the fundi normal. Visual acuity amounted to 5/5 (partly) — 5/4 (partly) in each eye after correction with +10 D sph \subset +0.5 D cyl, axis 90 for the right eye and with +0.75 D cyl, axis 90 for the left eye.

Accommodation was intact, as proved by objective (skiascopic) and subjective examinations. The patient's near point, with each eye examined separately, was 9 cm for the finest type of print. No accommodotonia (Franceschetti and Bichler¹) existed, i. e., there was no increase in the time interval between fixation for distance and fixation for reading at 25 cm.

1 Franceschetti, A, and Bichler, V. L'accommodotomie post-commotionnelle, son importance pour la pathogenese des symptomes oculaires dans l'encephalopathie post-traumatique, *Schweiz med Wchnschr* 71 433-436, 1941.

Pupillary Reactions—The pupils were of equal size. The reaction to light, both direct and consensual, was prompt and full. The near point reflex (when the patient was focusing on a near object, as already mentioned) was normal. When he was focusing on a near object with one eye, there was a consensual contraction of the pupil of the other eye.

Fields of Vision—Examinations, repeated several times by three observers over a period of five months, revealed concentric contraction of the fields and a ring

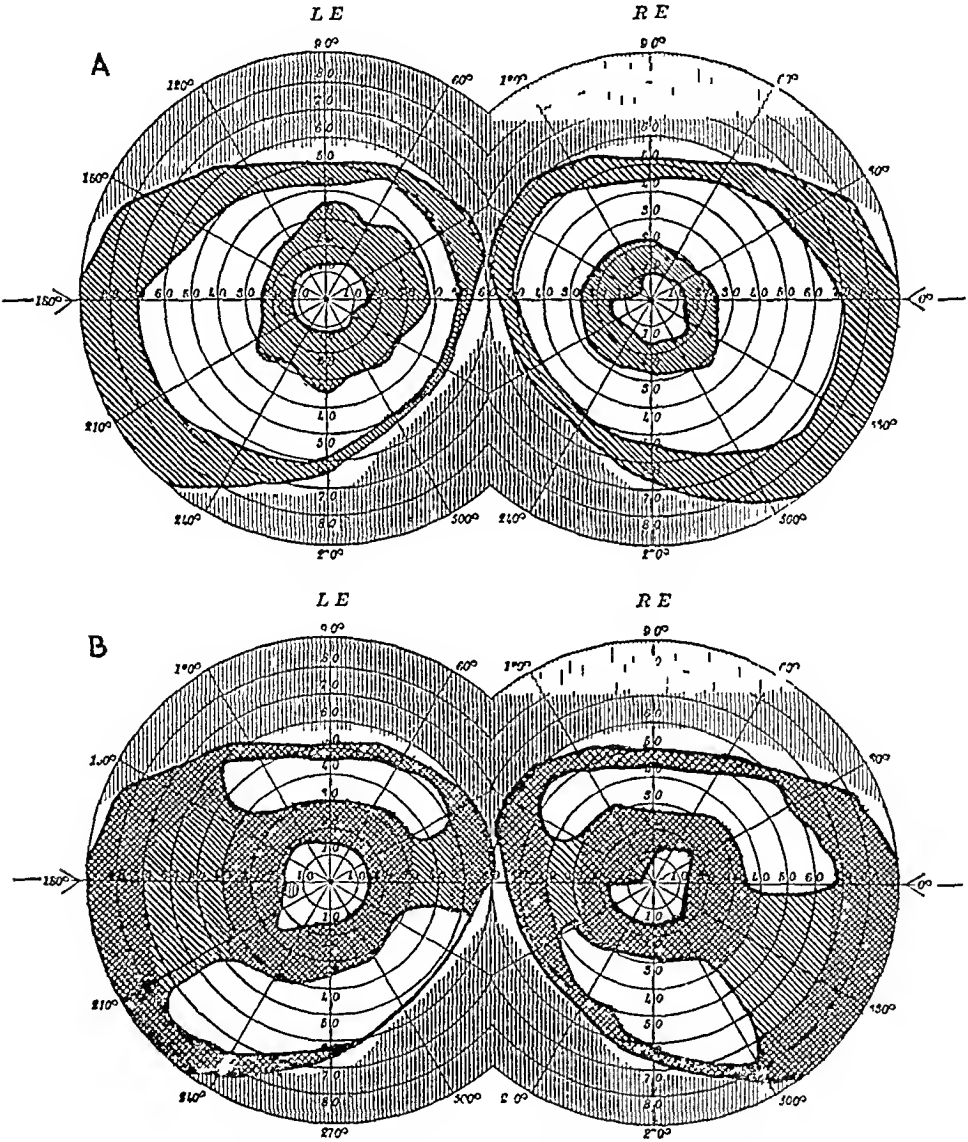


Fig 4—Field charts, (A, taken Dec 12, 1944, B, taken Feb 15, 1945), showing concentric contraction of the fields and ring scotomas, the latter being of different shape and extent in the two determinations. B, which is of a type found once only, even shows a certain amount of merging (relative scotomas) of the peripheral contraction and the annular scotoma.

scotoma in each eye, these scotomas were persistent, although changes in their shape and extent did occur from time to time (fig 4 A and B). While the concentric contraction was determined with the usual perimeter, the ring scotomas were taken on Bjerrum's screen at a distance of 1 meter.

COMMENT

Bielschowsky,² after enumerating the requirements for an unquestionable diagnosis of pure organic paralysis of convergence, emphasized the extreme rarity of the condition. He stated that of several thousand cases of ocular palsies of the most different types he was able to verify this condition in only a few.

In cases of postencephalitic states a relative frequency of paresis of convergence, often in conjunction with other motor disturbances, seems to exist, but in most of these cases the clinical picture does not comply exactly with the requirements for a sure diagnosis, namely (1) definite symptoms of an organic intracranial lesion, (2) history of sudden onset of the disturbance, (3) constancy of the symptoms at different periods and in various examinations and (4) unimpaired state of accommodation and near point reaction of the pupil in the absence of convergence. Our case meets these four requirements.

With regard to the diplopia presented by this patient the following statement can be made. It seems to be in the nature of a pure convergence paralysis that (for more or less near objects) the separation of the images is greater when the patient is looking straight forward than when he is looking sideways. Increase of separation while he is looking upward and decrease of separation while he is looking downward are due simply to anatomic factors, as was adequately explained by Bielschowsky, Adler and Spaeth.

In connection with this case, three main points lend themselves to discussion. First proof is again obtained of the independence of the so-called convergence reaction of the pupil of convergence and of accommodation. Thus, the term introduced by Behr³ (1924) for the contraction of the pupil usually associated with convergence of the eyeballs and with a greater or less degree of accommodation, namely, *Nahceinstellungsreaction*, or "near reaction" (in Duke-Elder's translation⁴) is sufficiently justified and should be generally adopted. This term is meant to indicate that in near vision contraction of the pupil in itself serves a useful optic purpose and is coordinated with the function of accommodation and the convergence of the eyeballs rather than subordinated to either of them.

2 Bielschowsky, A., in Bumke, O., and Foerster, O. *Handbuch der Neurologie*, Berlin, Julius Springer, 1936, vol. 4, p. 235, *Lectures on Motor Anomalies*. X. Supranuclear Paralysis, *Am J Ophth* **22**: 603-613, 1939.

3 Behr, C. *Die Lehre von den Pupillenbewegungen*, Berlin, Julius Springer, 1924, pp. 31-36.

4 Duke-Elder, W. S. *Text-Book of Ophthalmology*, London, Henry Kimpton, 1932, vol. 1, p. 554.

Next comes the question of localization of the cortical centers of convergence, which for physiologic, clinical and experimental reasons must be represented bilaterally (Sherrington, Duane⁵) Aside from vascular lesions, direct trauma to the relevant area of the brain seems best suited to produce an isolated paralysis of convergence It is remarkable, however, that only a few cases of this kind are recorded in the literature One was described by Peters⁶ (1889) After an injury to the head, a young man presenting a small scar which was not adherent to the bone at the occipital region of the skull showed a typical picture of convergence paralysis, moderate divergent squint of the right eye and normal fields of vision

The second case was described by Hayne⁷ (1896) A young girl received a severe bump on the top of her head by striking it against a heavy beam According to her report, the blow fell in the median line at the posterior border of the frontal bone, but nothing unusual could be detected in this locality Convergence paralysis without impairment of associated movements was observed The author himself did not believe that "so slight a blow could cause so complete a paralysis," but this opinion is not incontestable

The third case of probable traumatic origin was reported by Vandergrift and Losey,⁸ in 1922 Convergence paralysis associated with paresis of accommodation gradually developed after a severe roentgen ray burn at the occiput

Roper⁹ (1941), in his paper, to which the reader is referred for its exhaustive discussion of the problem and for the historical and bibliographic data it contains, did not cite more than these 3 cases of convergence paralysis of traumatic origin Thus the case reported by us is, to our knowledge, the fourth in a series which seems to have special significance in so far as in all of them a more or less reliably confirmed injury to the occipital region or its proximity was present This, in conjunction with what is known from the literature (Duane⁵), points to the occipital cortex as the region which most probably harbors the

5 Duane, A The Associated Movements of the Eyes Their Nerve Centers, Conducting Paths, Production, Varieties and Derangements, *Am J Ophth* **7**: 16-26, 1924

6 Peters, A Ueber Convergenzlähmung, *Centralbl f Augenh* **13** 225-229, 1889

7 Hayne, H W Report of a Case of Paralysis of Convergence Without Impairment of Associated Movements, *Arch Ophth* **25**: 329-332, 1896

8 Vandergrift, G W, and Losey, R R Paralysis of Convergence and Paresis of Accommodation, *Arch Ophth* **51** 405-407, 1922

9 Roper, K L Paralysis of Convergence, *Arch Ophth* **25** 336-353 (Feb) 1941

supranuclear centers of convergence in question, possibly situated in the peristriate areas—Minkowski's optomotor field—(Cords¹⁰)

Thus, this case of pure convergence paralysis after an injury in the occipital region of the head is most instructive in showing the independence of the near point reaction of the pupil of convergence and of accommodation and in its reference to the localization of the cortical convergence center. Furthermore, its association with a bilateral ring scotoma is also of sufficient interest to be discussed here.

This type of annular scotoma has nothing to do with the scotoma described by Fuchs,¹¹ in 1933, and by the other authors he cites, which is very small and is much closer to the fixation point (paracentral) and in most cases of which the lesion has definitely been localized in the macular region of the retina. A ring scotoma, such as was present in our case has been described by some authors (Inouye,¹² Woelfflin,¹³ Traquair¹⁴) as a functional (hysterical) disturbance, especially when presenting fluctuations (in shape and extent) at various examinations and when found together with a concentric contraction of the fields. But it is certainly no mere coincidence that a persistent, though fluctuating ring scotoma occurring after an injury to the head has been reported almost only in those rare cases in which the injury had affected the occipital region or its close neighborhood (Inouye,¹² Marie and Chatelin,¹⁵ Beauvieux,¹⁶ Villaret and Beaulieu,¹⁷ Kaltwasser,¹⁸ Euler,¹⁹ Pascheff,²⁰ Gelb and Goldstein,²¹ Leblond²²)

10 Cords, R. Ueber Hemianopsie, *Klin Monatsbl f Augenh* **76** 124, 1926

11 Fuchs, A. Ueber kleinste dauernde Ringskotome nach Verkehrsunfällen und paracentrales Skotom nach elektrischer Ohrprüfung, *Klin Monatsbl f Augenh* **91** 20-30, 1933

12 Inouye, T. Die Sehstörungen bei Schussverletzungen der kortikalen Sehspähre, nach Beobachtung von Verwundeten der letzten japanischen Kriege, Leipzig, W. Engelmann, 1909

13 Woelfflin, E. Ueber ein seltenes Gesichtsfeldsymptom bei Hysterie, *Arch f Augenh* **65** 309, 1910

14 Traquair, H. M. *An Introduction to Clinical Perimetry*, London, Henry Kimpton, 1942, pp 100 and 274

15 Marie, P., and Chatelin, C. Les troubles visuels dus aux lésions des voies optiques intracerebrales dans les blessures de l'encephale par coup de feu, *Bull Acad de med* **74** 535-543, 1915

16 Beauvieux, D. Les troubles visuels dans les blessures par coup de feu de la sphere visuelle corticale ou des radiations optiques, *Arch d'opht* **35** 410, 458, 560 and 617, 1916-1917

17 Villaret, M., and Faure-Beaulieu, M. Sur quelques varietes rares d'alteration permanentes du champ visuel par blessure craniocerebrale interessant la region occipitale, *Ann de med* **5** 556-565, 1918

18 Kaltwasser. *Kriegsverletzungen der Sehspähre*, Berlin, E. Ebering, 1920

19 Euler. Ein Fall von Ringskotom, *Klin Monatschr f Augenh* **66** 298, 1921

Of the authors mentioned, Euler¹⁹ and Gelb and Goldstein²¹—the latter emphasizing the inconstant character of the ring scotoma at various examinations, an observation also confirmed by our case—spoke of an abnormal fatigability of the visual organ. This seems to be the best available assumption. Thus the possibility should be admitted that some general (bilateral) damage to the visual cortex is at the root of this well characterized disturbance in the field of vision, occurring in fairly persistent association with an injury to the occipital region. A definite localization in the striate areas is quite improbable in the case of a bilateral annular scotoma—for obvious neuroanatomic reasons.

In this connection, however, the most significant case (the sixth) reported by Gelb and Goldstein must be cited. The patient had a head injury from shrapnel in the occipital region. A roentgenogram showed three foreign bodies larger than a pinhead in the skin of the occiput and one metallic splinter the size of a pea in the right occipital lobe of the brain. After initial left hemianopsia (not observed by the authors themselves), left hemiambyopia remained, with bilateral half-annular scotomas in the left part of the visual fields. Remarkably, these half-annular scotomas changed in that in repeated examinations they were found to be located at different distances from the fixation point.

In conclusion, the two assumptions made on the basis of this case, namely, (a) that the supranuclear convergence centers are situated in the close neighborhood of the cortical visual centers and (b) that some general damage to the latter must have produced the bilateral annular scotoma, not only point to a lesion in the same area but actually may be said to support each other.

SUMMARY

A case of convergence paralysis due to trauma in the occipital region is described.

Accommodation and the near point reaction ("convergence reaction") of the pupils were intact, the independence of the near point reaction of accommodation and convergence is once more stressed.

The localization of the supranuclear convergence centers in the occipital region of the brain near the visual cortex is confirmed.

20 Pascheff, C. Sehstörungen nach Hinterhauptverletzungen, *Letopis*, 1915, Die zerebralen Ringkotome und seltenere nervöse Augenstörungen nach Kriegsverletzungen am Kopf, *Arch f Augenh* 91 233-246, 1922.

21 Gelb, A., and Goldstein, K. Psychologische Analysen hirnpathologischer Fälle auf Grund von Untersuchungen Hirnverletzter VII Ueber Gesichtsfeldbefunde bei abnormer "Ermüdbarkeit" des Auges (sog "Ringkotom"), *Arch f Ophth* 109 387-403, 1922.

A remarkable finding in the field of vision of both eyes was a persistent, though inconstant, ring scotoma. Fatigability, caused by general damage to the striate areas, is assumed to be at the root of this disturbance in the fields, which seems fairly regularly to be associated with an injury to the occipital region of the head.

Dr. L. Halpern, neurologist at the Hadassah University Hospital, referred the case to us.

Hadassah University Hospital

22 Leblond, E. Un cas de scotome annulaire bilatéral d'origine traumatique, *Ann d'ocul* **161** 740-744, 1924.

KERATOCONJUNCTIVITIS SICCA AND BUCCOGLOSSOPHARYNGITIS SICCA WITH ENLARGEMENT OF PAROTID GLANDS

Report of Two Cases of Sjogren's Syndrome, with Pathologic Study of a Lacrimal Gland and the Parotid Glands in One Case

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SJOGREN,¹ in 1933, described a chronic disorder characterized by reduction in the secretions of the lacrimal and salivary glands with accompanying keratoconjunctivitis sicca, together with dryness of the mucous membranes of the mouth and the upper respiratory system. A persistent enlargement of the parotid glands sometimes occurs. The several publications of Sjogren on this subject have established the condition as a syndrome, now bearing his name. For a detailed description of the disease, reference should be made to the publication by Bruce,² who in 1941 reviewed the literature on keratoconjunctivitis sicca and described additional cases.

In 1943 Gifford, Puntenney and Bellows³ classified cases with evidence of deficient lacrimation into three groups. In group I there was lacrimal deficiency, with moistening of less than 15 mm in the Schirmer filter paper test after five minutes but with no corneal or associated changes. In group II there was fairly complete lacrimal deficiency with corneal and conjunctival changes only of such a degree as to be visible with the slit lamp and, as a rule, with no associated signs. Group III included cases of the typical Sjogren syndrome, with almost no lacrimal secretion in Schirmer's test and with conspicuous corneal and conjunctival changes and one or more of the extraocular signs of that syndrome, usually a deficiency of salivary secretion. The following 2 cases fall into the third group, or cases of greatest lacrimal deficiency, presenting the typical Sjogren syndrome.

From the Department of Surgery, the University of Rochester School of Medicine and Dentistry, and the Strong Memorial Hospital

1 Sjogren, H. Zur Kenntnis der Keratoconjunctivitis sicca (Keratitis filiformis bei Hypofunktion der Tranendrusen), *Acta ophth (supp)* **11** 1, 1933

2 Bruce, G M. Keratoconjunctivitis Sicca, *Arch Ophth* **26** 945 (Dec) 1941

3 Gifford, S R, Puntenney, I, and Bellows, J. Keratoconjunctivitis Sicca, *Arch Ophth* **30** 207 (Aug) 1943

REPORT OF CASES

CASE 1—History—A 46 year old white woman was first seen during April and May 1943, when she was in the medical service of Dr L A Kohn and Dr S W Smith. She complained of headaches, burning eyes, photophobia, dryness of the mouth, pains in the joints and generalized weakness. Since 1934 these symptoms had never entirely subsided, with exacerbations of increasing severity. Because of the irritation of her eyes, reading had been almost impossible, except for short periods, during the past six years. Her glasses had been changed once a year during this time.

A radical operation on the sphenoid sinus in 1933 and later radical drainage of the right maxillary sinus gave temporary relief from headaches. Cracking and occasional bleeding at the corners of the mouth appeared in 1937. The history of sore tongue extended over an indefinite number of years. The discomfort to her tongue, gums and mouth on eating acid fruits had forced elimination of these items from her diet. Her appetite was poor. Her weight fluctuated from 105 to 112 pounds (47.6 to 50.8 Kg). For several months during the preceding year she had received large doses of a preparation of vitamin B complex and riboflavin by mouth, without change in her symptoms.

The list of her lower teeth were removed at the age of 28, because of decay. Her dentures had never been comfortable. She had intolerance to fatty foods but otherwise no gastrointestinal symptoms. There was no known allergy or sensitivity to food. A chronic productive cough had been present for years, and thick mucus in the throat for one year.

In February 1942 the right parotid gland became swollen and tender, but the inflammation subsided spontaneously.

The onset of menses was at 16 years. These were regular and without symptoms.

There was no family history of a condition like the patient's or of other familial diseases.

Examination—The weight was 47.8 Kg, the height 165 cm, the pulse rate 85, the respiratory rate 16 and the blood pressure 104 systolic and 76 diastolic. The patient appeared well developed but somewhat emaciated and poorly nourished, and she looked chronically ill. She appeared about 15 or 20 years older than her stated age. Mentally, she was alert and cooperative. The hair was coarse and gray, a few scaling, red spots showed on the scalp. Subcutaneous fat was scant. The lacrimal glands were not palpable. Severe photophobia was present. The margins of the lids, the bulbar conjunctiva and the upper tarsal plates were mildly injected. The lower palpebral conjunctivas appeared red and a little thickened. There were long strings of elastic mucus in the lower conjunctival cul-de-sacs.

Thickly scattered over the lower two thirds of both corneas were fine filaments and points which stained with fluorescein. Only the epithelium was involved. On one examination, several slightly elevated, jelly-like areas were seen, with a large twisted filament attached to the center of each. The conjunctival vessels extended as loops over the limbus for 1 mm on the lower half of each cornea. No plaques or Bitot's spots were noted on the bulbar conjunctiva. A few fine, flakelike opacities were seen in the cortex of the lens. The fundi were normal. Vision was 6/7.5 in each eye. The Schurmer test for lacrimation showed moistening of 4 mm of the filter paper at the end of three minutes, in a normal control, 30 to 40 mm was moistened in the same length of time. All the sinuses could be transilluminated and were nontender.

The angles of the mouth were cracked and red. The tongue was slightly smooth, its color was normal. Papillae were present but smaller than usual. There was complete edentation. Atrophy was marked by almost complete absence of the lower alveolar ridge. Clear fluid could be expressed from the submaxillary ducts. The pharynx was slightly injected. No tonsillar tissue was visible. The mucous membranes of the mouth and pharynx were dry. The isthmus of the thyroid was readily palpable, with slight diffuse enlargement. The parotid and other glands in the neck were not palpable. No pigmentation or change in the skin was present over the extremities.

Except for slight bilateral enlargement of the phalangeal joints, the rest of the physical examination, including a neurologic and a pelvic examination, revealed no abnormalities.

Laboratory Tests and Special Examinations—A blood count showed 4,400,000 red cells, 13.3 Gm of hemoglobin per hundred cubic centimeters and 5,400 white cells, with a differential count of 65 per cent polymorphonuclear leukocytes, 32 per cent lymphocytes, 2 per cent neutrophils and 1 per cent eosinophils. The red blood cells were normocytic, no anisocytosis or poikilocytosis was noted. The platelet count was adequate. Examination of the urine and stools revealed nothing abnormal. The sputum was stringy, greenish yellow, thick and tenacious, with numerous white blood cells and a few cocci in clumps, pairs and short chains. No acid-fast organisms were found in concentrated specimens of sputum. The sputum was negative for Vincent's organisms. *Neisseria catarrhalis*, *Staphylococcus aureus* and *Escherichia coli* were cultured from the sputum. Streptococci of the viridans group and hemolytic staphylococci were cultured from material from the eyes. On Sabouraud's medium, *Candida* was repeatedly cultured from secretions from the mouth, but none were obtained from the eyes. Cutaneous tests for brucellosis with fat-free antigen, the old tuberculin test (dilution, 1:10,000) and the cutaneous test for *Candida* gave negative results. The Wassermann reaction of the blood was negative. The corrected sedimentation rate was 29 mm per hour. On the patient's second admission it was 43 mm per hour. The serum albumin measured 4.3 Gm, the serum globulin 3.2 Gm and the total protein 7.5 Gm, per hundred cubic centimeters. The nonprotein nitrogen of the blood measured 25 mg, the sugar 75 mg, the calcium 9.1 mg and the phosphorus 3.4 mg, per hundred cubic centimeters. The uric acid of the blood was 3 mg per hundred cubic centimeters. The cephalin flocculation test gave a 1 plus reaction. The blood amylase concentration was 69 units. The icteric index was 5. Gastric analysis revealed the presence of free acid, with a total acidity of 5.4 cc per hundred cubic centimeters in terms of tenth-normal sodium hydroxide. The basal metabolic rate was +12 per cent. The vaginal epithelium contained an adequate storage of glycogen, as demonstrated by the Lugol vapor method.

Determinations of the vitamin A content of the blood (Dr. A. McCord) revealed a fasting carotene content of 52 units and a xanthophyll content of 400 units, per hundred cubic centimeters. The fasting vitamin A level of the blood was 38 units per hundred cubic centimeters, at four hours after ingestion of 347,000 U. S. P. units of vitamin A, it measured 58 units, at six hours 200 units and at nine hours 127 units, per hundred cubic centimeters. A later determination showed somewhat similar figures. The vitamin C content of the blood was 0.69 mg per hundred cubic centimeters.

Roentgenographic examination showed that the sinuses were clear. Fluoroscopic and roentgenographic examinations of the chest suggested some emphysema, examination of the lungs with iodized poppyseed oil and a series of fluoroscopic studies of the gastrointestinal tract revealed no abnormalities, a roentgenologic

series of the gallbladder showed that the function of the gallbladder was rather low but apparently within normal limits

Wright's stain of one of the adherent corneal filaments, nearly 1 mm long, showed a twisted roll of thick mucus with numerous scattered epithelial cells. The stained mucus from the conjunctiva revealed occasional polymorphonuclear leukocytes and lymphocytes, globules of clear mucus and many squamous epithelial cells.

Treatment and Course—The puncta on the right were temporarily sealed by cautery, without improvement in the ocular symptoms. For one month the patient received a daily dose of 0.5 mg of diethylstilbestrol. During June 1943 she received daily 50,000 U S P units of vitamin A and 100 mg of mixed tocopherols. Administration of tocopherols was discontinued after one month, but the same daily dose of vitamin A was continued for three and a half months, when it was reduced to 10,000 U S P units for two months. In November 1943 the corneas stained profusely and filaments were present. Enteric-coated ammonium chloride in 2 or 3 Gm doses a day reduced the tenacity of the mucus in her throat. The patient's condition remained unchanged while she was under observation, except for apparently spontaneous periods of improvement.

CASE 2—This case was studied from the record of more than a hundred visits which the patient made to the clinics and the Strong Memorial and the Rochester Municipal Hospital over the period from August 1929 to March 1944.

History—In August 1929 a white woman aged 44 complained of feeling run down and of loss of weight. She had been depressed and reclusive after a thyroidectomy, at the age of 33, but since then had been in fairly good health. She was of a nervous, tense temperament, much given to worrying. During the previous winter her tongue had burned, as from canker sores. Her appetite had been good. Her mouth had been dry since the removal of her seventeen remaining teeth, at the age of 35. Examination at this time revealed that the conjunctivas were slightly pale, there were cracks at the corners of the mouth, the tongue was smooth, with no atrophy of the papillae, the pharynx was dry, and a few ulcers showed on the gums. The red blood cell count was 4,320,000 and the hemoglobin concentration was 60 per cent. In October 1929 the patient complained of a constant burning sensation over the tongue and lower part of the mouth, particularly when she ate, associated with dryness of the lips and mouth, an acid taste in the mouth and occasional peeling of the lips. The lower gums were described as overgrown and hypertrophied.

In December 1933 she stated that the soreness of the tongue and gums with dryness of the mouth had remained unchanged for four years. She had been treated elsewhere for a corneal ulcer. No apparent deficiency was found in her diet. Gastric analysis revealed no free hydrochloric acid after injection of alcohol or histamine. The red blood cell count was 4,500,000 and the hemoglobin content 68 per cent. The corpuscles exhibited marked central pallor, but there was no anisocytosis or poikilocytosis. The patient received iron and ammonium citrates and hydrochloric acid with meals. During March 1934 all the symptoms continued, and general weakness and slight numbness of the fingers were noted. Lesions of the lower lips were described as herpetic. She received pills of ferrous carbonate U S P, hydrochloric acid, cod liver oil and yeast. During June 1934 her eyes smarted and were red. Photophobia occurred for the first time in September 1934, together with burning and a thick discharge from the eyes. The lips were cracked, the gums, mucous membranes of the mouth and tongue were painful and burned. She continued to feel tired.

In November 1935 she had an acute attack of what was described as weeping dermatitis around her lip (fig 1A), lasting three weeks. This was the most severe attack she had had up to that time, and the condition cleared spontaneously. In January 1936 there was a recurrence, which cleared in a month. During the fall of 1936 her condition was somewhat improved, and she continued to receive iron, hydrochloric acid and yeast. A sensitivity to her dentures being suspected, new plates of different material were prescribed. The lesions in the mouth persisted. During March 1937 acid fruits in particular caused discomfort to the sore tongue and mouth. In August 1937 the right parotid gland suddenly became painful and swollen. A white, somewhat stringy secretion was present in her eyes in July 1938. From July to January 1939 she was fairly comfortable. The red blood cell count averaged 4,000,000 and the hemoglobin concentration was 80 to 90 per cent during this period. It was recorded that she was living on a very small income. Her appearance in April 1939 suggested to one examiner a deficiency in vitamins A and B, for which she received iron, yeast and a con-



Fig 1 (case 2)—A (November 1935), appearance at the height of a relapse. The mouth and the surrounding skin are red and peeling. B, May 1943. The right parotid gland had been enlarged for seven years. The conjunctivas are slightly injected. The angles of the mouth were cracked. (The apparent excess moisture in the eyes is an aqueous solution of butacaine sulfate, instilled to overcome the severe photophobia caused by the photographer's lights.) C, taken May 1943. The tongue is smooth, dry, slightly red and fissured. The papillae are flattened and reduced in size.

centrate of vitamins A, B and D. The symptoms referable to the lips, mouth and eyes had not lessened. In October 1939 the impression was that of riboflavin deficiency, she was given yeast and ferrous sulfate. At this time vision was 6/6 in each eye.

In November 1941 a clinical diagnosis of Sjogren's syndrome was made. She added to her history the statement that for about six years her eyes had become red and bloodshot when she "cried" although no actual tears were ever shed. For the past four years, on awakening in the morning she had been unable to see until she dropped salt water into her eyes. During the most severe episodes,

intense frontal headaches accompanied the sore eyes, making it necessary to close and cover the eyes to obtain any relief. Visual acuity was lowered during these severe attacks. Glasses had been worn since 1915. She had been conscious of night blindness to some degree for about ten years.

The right parotid gland had remained enlarged, firm and nontender since the acute attack in August 1937. Hearing was impaired in the right ear. Colds and sore throat were infrequent. Because comfortably fitting dentures were not obtainable, it was difficult for her to eat other than soft food. Her family considered her appetite poor and her eating habits erratic. During the periods when her mouth was sorest, discomfort made eating such an effort that she lost weight. However, during the thirteen years in which she was under observation her weight remained rather constant, at 42 to 43 Kg. There were no definite gastrointestinal symptoms. She had no cough, rheumatism or pain in the joints. For years she had had frequent nightmares, horrifying dreams and emotional outbursts.

Onset of menstrual periods occurred at the age of 17; they were irregular and symptomless. The menopause, at the age of 51, was gradual in occurrence and asymptomatic.

A sister, with pernicious anemia, and their mother had severe arthritis. The average age at which the other members of the family lost their teeth was 60 years. No family history of symptoms resembling the patient's or of other familial diseases was known.

Five intravenous injections of 5 mg of riboflavin each were given during one week and were not followed by any appreciable change in symptoms. Potassium iodide was taken by mouth. Liquid petrolatum U. S. P., butacaine and phenacaine gave temporary relief to the eyes. A conjunctival culture revealed diphtheroids and a hemolytic *Staph. aureus*. During December 1941 filamentous tags were seen on the left cornea. Daily the patient received 30,000 U. S. P. units of vitamin A and 570 units of vitamin D in the form of halibut liver oil; during February 1942 she received, in addition to the halibut liver oil, yeast, riboflavin, nicotinic acid and thiamine hydrochloride, by mouth. Her general appearance continued to grow worse throughout the spring and summer of 1942. In December 1942, in a gastroscopic examination, the gastric mucosa was described as cobblestone in appearance and typical of hypertrophic gastritis. For three months, though she was receiving a daily oral dose of 5 mg of riboflavin and 3 Gm of brewers' yeast, she showed no notable change. During April 1943 she received four weekly intramuscular injections of a preparation of the vitamin B complex, containing 10 mg of thiamine hydrochloride, 5 mg of riboflavin, 5 mg of pyridoxine hydrochloride, 5 mg of nicotinic acid and 50 mg of sodium pantothenate, with no improvement. While she was under this treatment, acute left parotiditis developed, for which she was admitted to the hospital, in April 1943, to the medical service of Dr. L. A. Kohn and Dr. S. W. Smith.

Examination—The weight was 43 Kg., the height 154.5 cm and the pulse and respiratory rates 100 and 16 per minute, respectively. The blood pressure was 122 systolic and 68 diastolic. The patient was a small, thin, wiry woman, aged 59, she appeared moderately ill and rather apathetic but was mentally alert and cooperative. Below each ear was a swelling of the parotid gland. The mass on the left side was extremely tender, that on the right was firm, slightly lobulated and nontender. No fluctuation was demonstrable, nor could material be expressed from the parotid ducts. Vision with correction was 6/15+1 in the right eye and 6/12—2 in the left eye. The skin of the upper lids and of the margins of the lids was red. Below each inner canthus appeared an area, measuring 1 cm., of slightly reddened, scaling skin. The outer canthus was red,

fissured and scaling. Photophobia was severe. The lacrimal glands were not palpable. The palpebral mucosa in each eye was red and smooth but slightly thickened and edematous. The bulbar conjunctivas were slightly injected. There were no plaques or areas suggestive of Bitot's spots. In the conjunctival sacs were strings of white, elastic, mucoid material. Punctate areas, staining with fluorescein, were sharply limited to the lower halves of the corneas. No filaments were visible.

Examination with the slit lamp revealed superficial conjunctival vessels passing over the limbus on the lower half of each cornea in loops for a distance of 3 to 4 mm and across the upper limbus for 1 mm. Numerous fine, flakelike opacities were visible in the anterior cortex and around the anterior Y sutures. The nucleus was slightly yellowish.

The maculas and optic disks were normal. The retinal arteries were slightly sclerotic. In an area of 3 to 4 disk diameters surrounding each disk, but not in the macular region, were scattered yellowish spots of 1 to 2 vein diameters, some of which were confluent and appeared to be in the anterior layers of the retina. Most of these spots were near vessels. In the periphery of the retinas were scattered whitish streaks of atrophy with fine black pigment granules. In the Schirmer filter paper test, 3 to 6 mm was moistened in each eye at the end of two minutes, whereas the average area for a normal control was 20 mm. The tears turned red litmus slightly blue. Color vision as tested with Ishihara charts was normal.

The drum membranes were normal. Air conduction was absent on the right and diminished on the left. The skin at the corners of the mouth was reddened and cracked. Edentation was complete. Small, whitish elevations of macerated epithelium, which were easily denuded, leaving a bleeding spot of pinpoint size, were scattered over the mucous membranes of the mouth. The tongue was smooth, shiny, slightly red and fissured. The papillae were flattened and reduced in size (fig 1 C). The tongue was painful to the touch. The buccal mucous membranes were also smooth, shining and dry. The tonsils were slightly hypertrophied. The saliva changed blue litmus red. A thick, white, creamy material could be expressed from the submaxillary duct. The thyroid was not palpable beneath a surgical scar above the sternum. Cervical glands were palpable as small, shotty and non-tender masses. The submaxillary salivary glands were not palpable. The rest of the physical examination, which included pelvic and neurologic examinations, revealed a state consistent with the age of the patient.

Laboratory Data—Studies of the blood revealed 4,910,000 red cells, 12.5 Gm of hemoglobin per hundred cubic centimeters, 12,900 white cells, 2.2 per cent reticulocytes, a hematocrit reading of 39.1 per cent and a differential count of 71 per cent neutrophils, 2 per cent eosinophils, 20 per cent lymphocytes and 7 per cent monocytes. There was no poikilocytosis, anisocytosis, polychromatophilia or stippling. The corpuscles showed slight central pallor. The number of platelets was adequate. The urine was normal. The stool gave a negative reaction to the guaiac test, and culture revealed no pathogens. The Wassermann reaction of the blood was negative. The corrected sedimentation rate was 34 mm, and a later one was 40 mm, per hour. The fasting blood sugar measured 80 mg per hundred cubic centimeters. The urine gave a negative reaction for sugar during this test. Chemical analysis of the blood revealed 10.7 mg of calcium, 4.4 mg of phosphorus, 29 mg of nonprotein nitrogen. 619 Gm of total plasma proteins. 3.8 Gm of albumin and 3.1 Gm of globulin, per hundred cubic centimeters. The reaction to the cephalin flocculation test was 1 plus. The blood amylase content was 130 units. Agglutination tests for brucellosis gave negative results. Tests

for brucellosis with fat-free antigen, the tuberculin test and cutaneous tests for *Candida* gave negative reactions. Gastric analysis revealed no free fasting hydrochloric acid and none after injection of alcohol or histamine. Microscopic examination revealed nothing abnormal, aspiration of the duodenal contents yielded 5 cc of slightly bile-tinged fluid, normal bile fractions were obtained after introduction of 300 cc of saturated magnesium sulfate. Cultures of material from the throat yielded *Hemophilus influenzae* predominantly. *Candida* was isolated from pus from the submaxillary gland and the mouth. None were found after repeated cultures of conjunctival secretion. The basal metabolic rate was —10 per cent.

Roentgenographic Examination—The mandible showed normal bone density, with absence of the alveolar ridge. Roentgenograms of the chest and a series of fluoroscopic studies of the gastrointestinal tract showed nothing abnormal. There was no arthritic change in the hand. An oral cholecystogram suggested diminished power of concentration of the gallbladder.

Special Examinations—Strands of mucus from the eye, stained with Wright's method, were largely composed of clear strings and globules of mucus, with many small lymphocytes in various degrees of disintegration and occasional squamous epithelial cells. Pus from the submaxillary ducts was loaded with small lymphocytes and polymorphonuclear leukocytes.

Determinations of the vitamin A content of the blood (Dr A. McCord) gave the following values:

	Patient's Values, Units/100 Cc	Normal Values, Units/100 Cc
Vitamin A	14	15 - 30
Carotene	36	75 - 150
Xanthophyll	14	40 - 80

The vitamin C measured 0.70 mg per hundred cubic centimeters (normal, 0.70—1.5 mg per hundred cubic centimeters).

Determinations of the absorption of vitamin A for nine hours after ingestion of 347,600 U. S. P. units of vitamin A in the form of halibut liver oil gave the following values:

	Patient's Values, Units/100 Cc	Normal Values, Units/100 Cc
Carotene	26	
Xanthophyll	14	
Vitamin A		
Basal	14	25
4 hours	39	227
6 hours	42	154
9 hours	44	71

Dark Adaptation Threshold—Determinations on different occasions, (Dr E. Millard) were as follows:

	Milliamperes
Both eyes	log 4.11
Right eye	log 4.39
Both eyes	log 3.85
Normal range	log 3.40-4.00

Treatment and Course—The swelling of the left parotid gland disappeared after three doses of 100 units of roentgen radiation of low voltage. Biopsy of the right (fig. 2) and the left (fig. 3) parotid gland was done two weeks after the acute parotiditis on the left side had subsided. A biopsy specimen of the orbital portion of the left lacrimal gland (fig. 4) was removed through a cutaneous incision. Biopsy of a specimen of the lower palpebral conjunctiva of the left eye, consisting of a strip of stratified squamous epithelium, showed hyperplasia in

several places. No hydropic degeneration of the epithelium was present. There were several mitotic figures. The underlying loose connective tissue contained numerous chronic inflammatory cells composed chiefly of plasma cells.

Contact lenses were well tolerated for one and a half hours. During her hospitalization, the patient was treated with vitamin concentrates. All her symptoms improved. On her discharge from the hospital, she received daily a vitamin B complex preparation containing the equivalent of 15 mg of thiamine hydrochloride, 0.5 mg of riboflavin and 5 mg of nicotinic acid, 6 Gm of brewers' yeast extract, 25,000 U S P units of vitamin A and 475 units of vitamin D in the form of halibut liver oil, 100 mg of mixed tocopherols, and 10 mg of ascorbic acid.

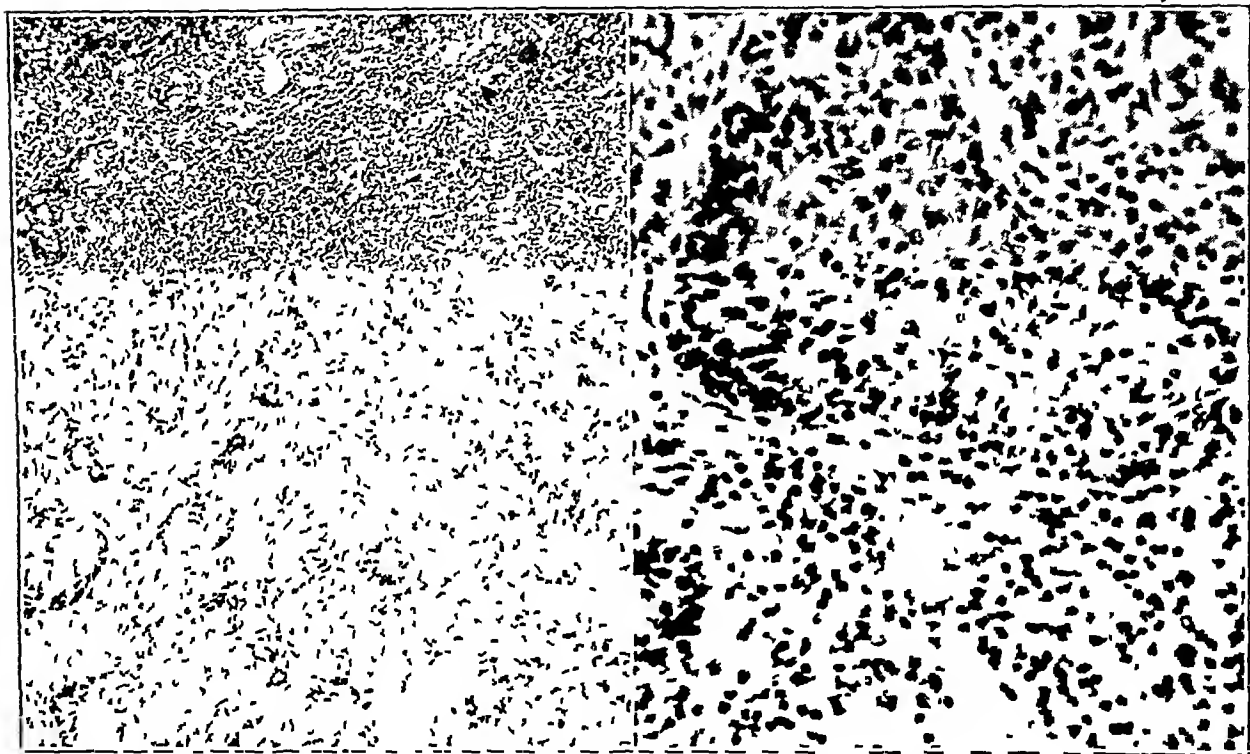


Fig 2 (case 2)—Biopsy specimen from the right parotid gland, consisting of a mass of lymphoid cells within a fine stroma of connective tissue. There are several islands of highly irregular cells with hyperchromatic nuclei, some of these islands have an irregular arrangement. Masses of hyalin-like substance are scattered throughout the section. This change in the gland has replaced the normal structures, so that no glandular tissue is seen. A Gram stain (at right) showed no organisms and contributed nothing further to the diagnosis.

During the spring and summer of 1943 she complained of increased fatigability, sore eyes and sensitivity to light. An infection of the upper respiratory tract during the winter accentuated all symptoms.

In March 1944 the area of reddening around her mouth, which was composed of fine, weeping vesicles, had increased to 3 or 4 cm, discomfort and weakness of the eyes had increased. Her general condition was worse than during the previous winter. The submaxillary ducts were filled with creamy pus. Material from a needle puncture of the enlarged right parotid gland cultured on Sabouraud's medium and blood agar yielded no growth. *Candida* was cultured from material

taken from the cracks at the angles of the mouth. Only *Staphylococcus albus* and *Staphylococcus citreus* were obtained from cultures of the surrounding reddened skin.

COMMENT

When the first patient was 37, her eyes became irritated, while the second patient complained of a sore mouth at the age of 44, at which age her mouth had already been dry for nine years. For nine and fifteen years respectively the patients had had constant and increased irritation of the eyes together with cracking at the corners of the mouth and irritation of the buccal mucous membranes and tongue, which were accompanied with dryness of the mouth. None of these complaints

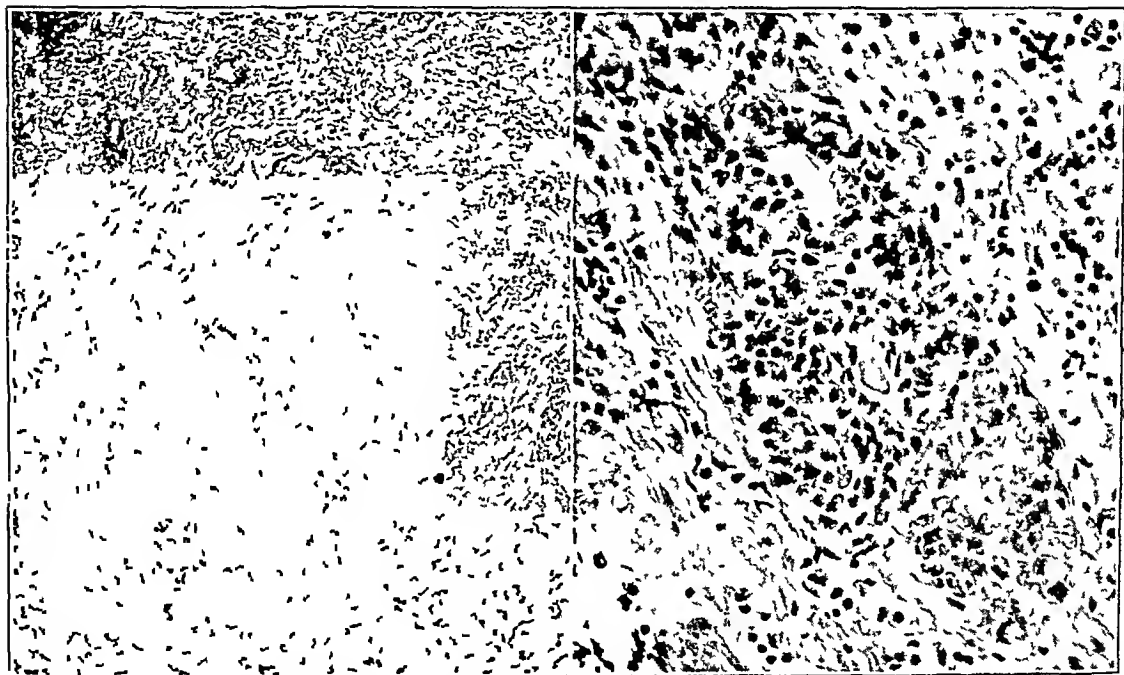


Fig 3 (case 2) —Biopsy specimen from the left parotid gland. The glandular tissue is entirely replaced by masses of lymphoid cells, similar to those seen in the right parotid gland. There are several clumps of undifferentiated cells, each having a vesicular nucleus. These clumps of cells, each with a central space, seem to be replacing a parotid duct. A few acute inflammatory cells are seen here and there. No giant cells were noted.

has ever completely disappeared but has become progressively worse, with periods, usually during the winter months of greatly accentuated symptoms. Both patients had had acute parotiditis, the right parotid gland of the second patient had remained enlarged for seven years.

The unfortunate victims of this disease like most persons with chronic disease, search ceaselessly for relief. The first patient had been under medical care for nine years, the second made more than one hundred visits to the hospital clinic over a period of fifteen years.

Sjogren's syndrome has been considered by some investigators to be a result of the lowered endocrine function accompanying the menopause. The activity of the disease in these 2 patients occurred at an earlier age.

One of the complications observed in other patients whose cases have been reported is the advanced dental caries. Cheyne⁴ showed that a disturbance of normal salivary flow in rats in which the salivary glands had been removed resulted in an increase of experimental caries directly in proportion to the amount of serous saliva removed. The early age at which dental caries occurred, requiring total extraction of the teeth

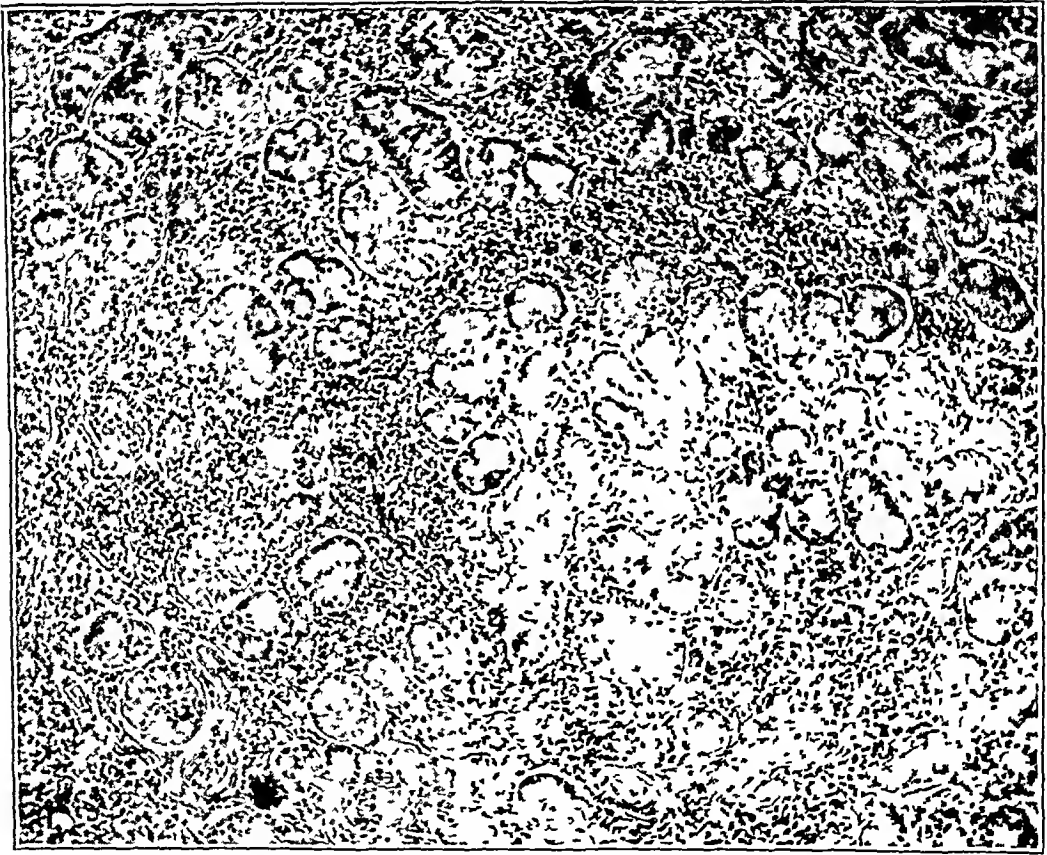


Fig 4 (case 2) —Biopsy specimen from the left lacrimal gland. Here, the usual acini of glandular tissue are seen. Between the acini there is an infiltration of numerous lymphocytes. Thick, hyalin-like substance, dense connective tissue and reticular tissue are also seen between the acini.

in case 1 at the age of 28 and in case 2 at the age of 35, suggests that there was decreased salivation of a degree sufficient to produce dental caries even before the symptoms of a dry mouth were manifest to the patient. Pathologic changes in the salivary glands of these 2 patients may therefore have long antedated their first symptoms.

⁴ Cheyne V. D. Effects of Selective Salivary Gland Extirpation upon Experimental Dental Caries in Rats. *Proc Soc Exper Biol & Med* 42:587 (Nov.) 1939.

Since the parotid gland is the main source of the serous saliva, with the parenchyma of these glands destroyed (figs 2 and 3) there is little wonder that one of the most annoying complaints is a dry mouth. Only limited function of the lacrimal gland can be expected with the change in the glandular structure and the chronic inflammation (fig 6). The infiltration of lymphoid cells, with changes in the connective tissue and destruction of the parenchyma of these glands, is the characteristic pathologic feature of this disease. No infectious etiologic agent for this reaction could be found either in the glands themselves or in a more distant focus. The presence of *Candida* in the mouths of both patients would seem to be only incidental to the abnormal state. Sjogren found almost complete destruction of the parenchyma of the lacrimal glands in patients he examined⁵. He studied the sublingual, palpebral and accessory lacrimal glands and the glands of the nasal mucous membrane, pharynx and lips, where the same pathologic process was found.

If similar abnormalities exist in the epithelium and the glandular structures throughout the intestinal tract, interference with normal digestion and normal alimentary absorption is to be expected. This could cause a variety of superimposed chronic deficiencies, contributing to the complex clinical and laboratory picture.

The chronic inflammation of the mucosa of the upper respiratory system, which is covered with a sticky mucous secretion, is probably shared by the accessory air sinuses and their drainage channels. On the basis of this pathologic condition, an explanation of the sinusitis of the patient in case 1 is possible. A third woman with the typical syndrome, who was seen by one of us, had had several operations on the sinuses over a period of years because of severe, persistent frontal headaches. She had also received treatment for chronic eustachitis. Pansinusitis, eustachitis and mastoiditis occurred in cases reported by Bruce². Apparently, the otolaryngologist is consulted as frequently by these patients as is the ophthalmologist.

The 3 patients with Sjogren's syndrome whom we observed were women of slender build and nervous, excitable temperament. There has been no mention in the literature of any constitutional type peculiar to this disease.

The vitamin A level of the blood and the absorption curve in case 1 were normal. In case 2 both the vitamin A level of the blood and the absorption curve were low, the biophotometric measurements were within normal limits. Evidence of a vitamin A deficiency was not clinically outstanding. The presence of avitaminosis A was suspected.

5 Sjogren, H. Zur Kenntnis der Keratoconjunctivitis Sicca. III. Mikroskopische Veränderungen der Nasendrüsen. *Acta ophth* **13** 40, 1935, IV. Mikroskopische Untersuchungen über das Initialstadium der Drüsenveränderungen, *ibid* **16** 70, 1938.

and investigated in some of the cases reported in the literature. Acknowledging the controversy concerning the etiologic factors, Jegheis⁶ included Sjogren's syndrome with disorders due to vitamin A deficiency largely on the strength of Stahel's⁷ case, in which improvement followed vitamin A therapy. This case was complicated by advanced polyarthritis deformans. Bruce² failed to find biophotometric evidence of vitamin A deficiency in his most typical case. Gifford, Puntenney and Bellows,³ finding no deficiency of vitamin A in the blood in some of their cases, expressed the belief that vitamin A was rarely a factor in the condition. Deficiencies in vitamins A and C were carefully excluded in a case reported by MacLean.⁸ From the present evidence, we must conclude that avitaminosis A is an inconstant finding in cases of Sjogren's syndrome.

Clinically prominent in our 2 cases was the implication of a deficiency of members of the vitamin B complex, with many of the signs and symptoms attributed to an extreme degree of ariboflavinosis.⁹ Because of the presence of these signs, the 2 patients received treatment repeatedly, although unsuccessfully, with yeast, vitamin B complex concentrates and riboflavin. Assuming that these signs are caused by a lack of riboflavin, there may exist a faulty absorption of this vitamin in the intestinal tract or an inability to utilize it. An inadequate diet alone could modify or contribute to such a deficiency but does not satisfactorily explain the predominance of the reported cases of this disease in females, unless some further factor of sex is responsible. No studies of the incidence of ariboflavinosis relative to sex are available. Twenty-one of the group of 29 hospitalized patients and outpatients presented by Sydenstricker and associates^{9a} as manifesting riboflavin deficiency were females. This series, admittedly, is too small to permit more than suggestive conclusions.

A point of interest is the relative freedom from cataractous changes in these 2 cases and in other reported cases.

For evaluation of therapeutic response, the patients with less severe symptoms, although presenting a less striking clinical picture, would make better subjects than patients with the complete syndrome, in

6 Jegheis, H. Skin Changes of Nutritional Origin, *New England J. Med.* **228** 715 (June 3) 1943.

7 Stahel, W. Das Sjogrensche Syndrom eine A-Hypo-Vitaminose, *Klin. Wchnschr.* **17** 1692 (Nov. 26) 1938.

8 MacLean, A. L. Sjogren's Syndrome, *Bull. Johns Hopkins Hosp.* **74** 219 (March) 1944.

9 (a) Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M., and Kruse, H. D. The Ocular Manifestations of Ariboflavinosis, *J. A. M. A.* **114** 2437 (June 22) 1940. (b) Bicknell, F., and Prescott, F. *The Vitamins in Medicine*, London, William Heinemann, 1942, pp. 228-258.

which the late changes have confused the primary pathologic process and some tissues are permanently damaged

The numerous complications in the development of this disease do not occur in every patient, but the high incidence of each warrants the belief that they involve many of the body's systems of which the ocular manifestations are but a part. In the presence of a chronic inflammation of the lacrimal gland, the forms of local treatment of the eyes suggested up to the present must be considered of no more than palliative value.

SUMMARY

Two cases of Sjogren's syndrome are reported. The microscopic pathologic changes in a lacrimal gland and the parotid glands in 1 case are described. Some of the complications and attributed causes of this disease as one of wide systemic involvement are discussed. A clinical resemblance to advanced chronic riboflavinosis is noted.

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VASCULAR DISEASE ASSOCIATED WITH ANGIOID STREAKS OF THE RETINA AND PSEUDOXANTHOMA ELASTICUM

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AND

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DURING the past two years angioid streaks of the retina have been seen in 3 patients, in 2 of whom pseudoxanthoma elasticum was also present. In these 2 patients severe vascular disturbance was found in all the extremities. Since no mention of a relationship of these three conditions has been found in the available literature and since the association is probably significant, the cases are being reported.

The condition referred to as angioid streaks of the retina was first described by Doyne¹ in 1889. Since that time this condition has been found to be related clinically to two other degenerative diseases, (1) pseudoxanthoma elasticum and (2) osteitis deformans (Paget's disease). The relation to pseudoxanthoma elasticum was first noticed by Groenblad and Strandberg² in 1929.

Pseudoxanthoma elasticum is a degenerative disease of the skin, first reported by Balzer,³ in 1884. Scholz,⁴ reviewing the cases of angioid streaks appearing in the literature since the report of Groenblad and Strandberg,² found the two lesions to be associated in 59 per cent of all cases of angioid streaks. Similarly, Sandbacka-Holmstrom stated⁵ in his analysis of 100 cases of pseudoxanthoma elasticum found in the literature, that 87 also had changes in the fundus typical of angioid streaks of the retina.

The coexistence of osteitis deformans and angioid streaks of the retina is also noteworthy. This relationship was first noted by Rowland⁶ in 1929. In 1932 Terry⁶ reported 4 new cases and 5 additional ones gathered from the literature to establish the syndrome further. The occurrence of osteitis deformans and angioid streaks of the retina in the same patient was seen in only 9 per cent of the cases of angioid streaks.

1 Doyne, A. W. *Tr. Ophth. Soc. U. Kingdom* **9** 128, 1889.

2 Goedbloed, J. Syndrome of Groenblad and Strandberg, *Arch. Ophth.* **19** 1 (Jan.) 1938.

3 Cited by Scholz.⁴

4 Scholz, R. O. Angioid Streaks, *Arch. Ophth.* **26** 677 (Oct.) 1941.

5 Rowland, W. D. *Am. J. Ophth.* **16** 61 1933.

6 Terry, T. L. *Tr. Am. Ophth. Soc.* **32** 555 1934.

Angioid streaks of the retina is a condition of some rarity. Scholz,⁴ reviewing the literature in 1941, found 182 cases and added 6 of his own. The retinal picture is characteristic. It consists of pigmented streaks, radiating spokelike from a similarly pigmented ring which encircles the disk. This ring may be complete or incomplete and may be formed by a single pigmented line around the disk, or it may be made up of several interlacing lines of pigment. It may encircle the disk closely, with only a small width of retina intervening, or the ring may be $\frac{1}{2}$ disk diameter or more away. The radiating streaks may vary in width from minute to several times the diameter of the retinal arteries. Their borders are serrated. Their color has been reported in the literature most commonly as brown to reddish brown but has been described also as red, black, white and grayish brown. The retina between the streaks may show scattered pigmentation. Disciform degeneration (Kuhnt) and retinitis circinata are not uncommonly associated.

Pseudoxanthoma elasticum is an abnormality of the skin manifest by yellowish patches, the size of a pinhead to that of a pea, with roughening of the skin much like the striae atrophicae of pregnancy. Although the clinical relationship of angioid streaks of the retina and pseudoxanthoma elasticum was definitely established, it was not until the studies of Bock,⁵ in 1938, and Hagedoorn,⁷ in 1939, that a definite pathologic relationship was accepted. Although it had previously been known that pseudoxanthoma elasticum was due to a degeneration of elastic tissue fibers of the skin, it remained for these men to demonstrate that the retinal changes occurred on a similar basis and that both were probably part of a process widespread throughout the body. They demonstrated, in separate pathologic studies of tissues obtained at autopsy in cases in which the diagnosis of angioid streaks of the retina had been made before death, that the ocular condition was due to a degeneration of the elastic tissue fibers in Bruch's membrane, with ruptures in the membrane which corresponded to the location of the angioid streaks. They also found degeneration of the elastic tissue fibers of the smaller arteries and of the aorta. In each of their cases pseudoxanthoma elasticum was also present.

Obstruction of peripheral blood vessels or serious circulatory disturbance has not previously been reported. The only suggestion of such an observation in the available literature was noted in case 3 reported by Scholz, in which the absence of vascular pulsations in the lower extremities of a man aged 46 was noted. Apparently, no significance was attached to this finding. The following 3 cases of angioid streaks of the retina are reported, in 2 of which there was clinical evi-

⁷ Hagedoorn, A. Angioid Streaks, *Arch Ophth* **21** 746 (May), 935 (June) 1939.

dence of circulatory disturbance in the extremities, while in 1 case hypertension was present

REPORT OF CASES

CASE 1—A mess sergeant aged 26 was admitted to the ophthalmologic section on May 17, 1943, because of a bilateral, moderately severe burn of the eyes, incurred from a welder's arc. Vision was 20/20 in each eye. The visual fields were normal. Examination of his eyes revealed, in addition to the injury, a typical picture of bilateral angioid streaks of the retina (fig 1). He also had the classic cutaneous changes of pseudoxanthoma elasticum over the lower part of the face, the lips and neck, the upper portion of the chest and the axillas, where the skin fell into folds instead of retracting normally. This was noted only after the changes in the fundus led to its recognition (fig 2). Peculiar grooves or fissures resembling rhagades were noted on his lips, which he stated had appeared during the preceding three years. His past medical history revealed one significant complaint. He stated that he had never, even as a child, been

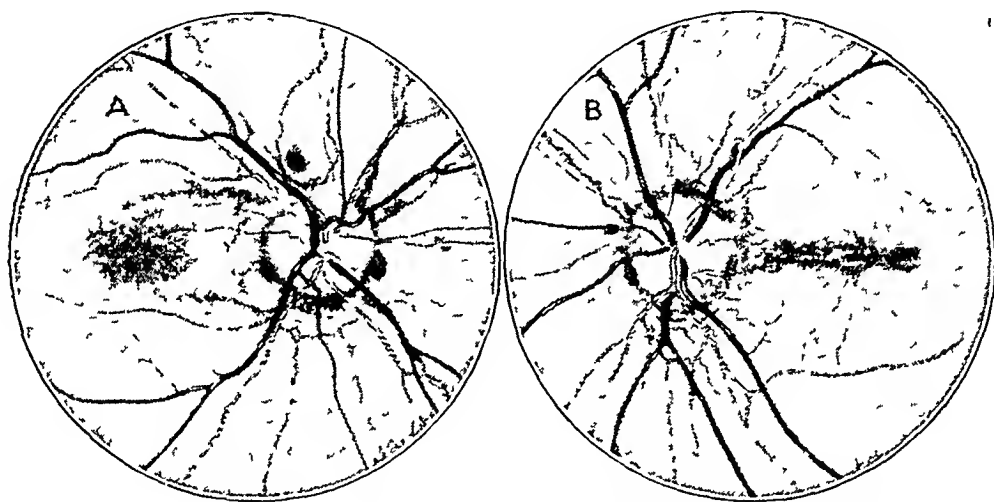


Fig 1 (case 1)—Drawings of the fundus, showing angioid streaks

able to walk as fast as other people because of cramps in his legs after walking short distances. This symptom had increased in severity as he became older until his exercise tolerance at present was about five minutes of close order drill, or three quarters of a mile (1.2 kilometer) at 120 steps per minute. He was also bothered by frequent cramps in his legs and feet at night. General physical examination revealed absence of the posterior tibial, dorsalis pedis and right ulnar pulses, the latter of which was confirmed by the reactive hyperemia test. The radial pulse was diminished in volume. His feet were small, requiring only a 4½ size shoe. Because of the absence of the pulses, oscillometric tracings were made by one of us (N E F). These revealed notable changes (fig 3A). Pulsation was practically absent at both ankles and the right wrist, slightly more perceptible at the thighs and about one-third normal at the left wrist.

The results of laboratory studies follow. A complete blood count and urinalysis, including concentration tests, gave normal results. The Kahn reaction of the blood was negative. The serum calcium measured 10.5 mg per hundred cubic centimeters, and the blood cholesterol was normal. Roentgenograms of his chest, skull and thighs revealed no evidence of Paget's disease, but shadows

of calcified vessels were found in the thighs (fig 4A). An electrocardiogram was normal. Consent was obtained and biopsy specimens from the left ulnar vessels and the skin were taken.

CASE 2—A soldier aged 23 was admitted to the hospital May 5, 1944 because of asthma and mild arterial hypertension. His complaints were mainly nervousness and anxiety, attributed to increasing severity of his asthma. No history of



Fig 2 (case 2) —Changes of pseudoxanthoma elasticum in the skin

circulatory difficulty was obtained. Physical examination revealed nothing abnormal except for rales and rhonchi throughout both lungs and hypertension, the blood pressure being 160 systolic and 110 diastolic. Vision was 20/20 in each eye without correction. External examination revealed nothing abnormal. The fundi revealed slight narrowing of the smaller arterial branches, as well as typical angioid streaks of the retina in each eye. The skin was normal.

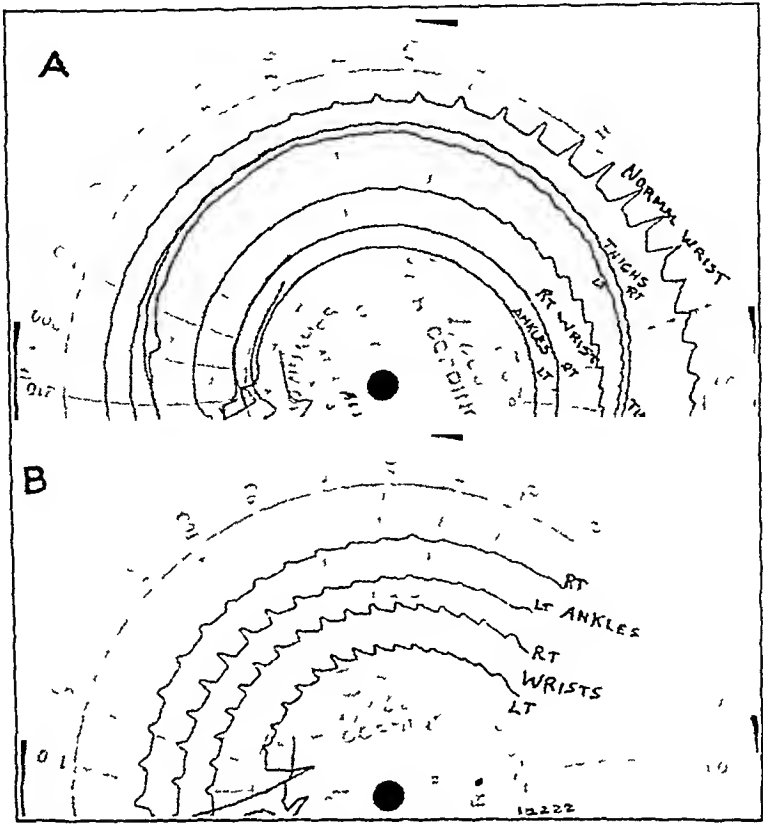


Fig 3—Oscillometric tracings (A) in case 1 and (B) in case 3, showing diminution in amplitude of pulsation as compared with the normal (A)

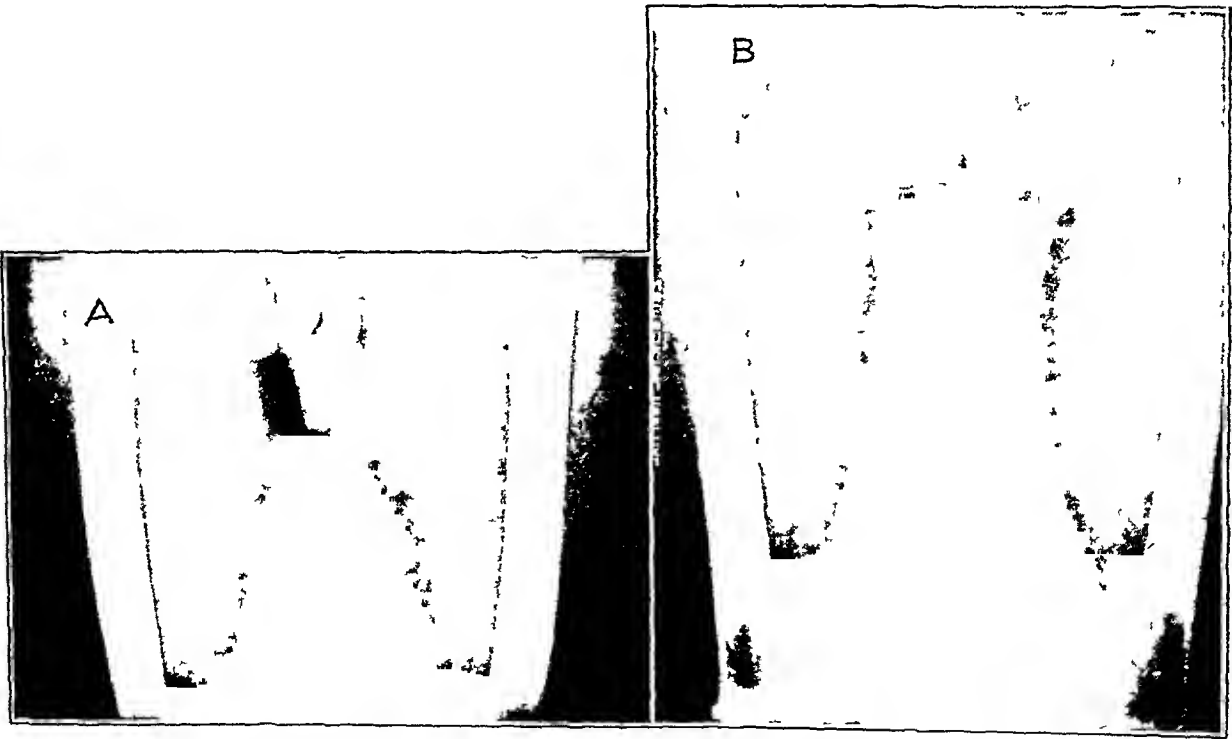


Fig 4—Calcified vessels in the thighs, as demonstrated by roentgenograms (A) case 1, (B) case 3

CASE 3—A 23 year old soldier came to the ophthalmologic clinic May 20, 1944 for refraction. Vision was 20/100 in the right eye and 20/200 in the left eye without correction. Vision of 20/20 was obtained with correction of a -1.75 sphere for the right eye and 20/20 with a -2.25 D sphere for the left

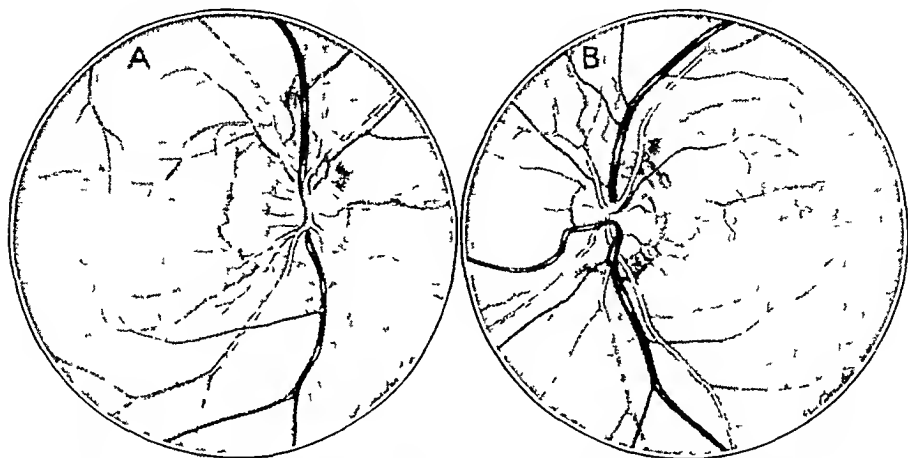


Fig 5 (case 3)—Drawings of the fundus showing angioid streaks



Fig 6 (case 3)—Changes of pseudoxanthoma elasticum in the skin

eye. External examination revealed nothing abnormal. Examination of the fundus revealed a well developed picture of angioid streaks of the retina in each eye (fig 5). The visual fields were normal. The skin of the upper part of the chest and the neck and axillae showed the early changes of pseudoxanthoma elasticum.

(fig 6) Even though no history of circulatory difficulty could be obtained, pronounced vascular changes were found on physical examination. The left posterior tibial pulse was absent. The dorsalis pedis pulse was good. The ankle pulse on the right was reduced in volume, as were both radial pulses. Both ulnar vessels were occluded, as confirmed by the reactive hyperemia test. Oscillometric readings by one of us (N E F) showed a generally diminished amplitude of pulsation, especially in the right ankle (fig 3 B). The patient was admitted to the hospital for study. His blood pressure was 130 systolic and 70 diastolic. The general physical examination showed a normal condition except for the changes noted. A complete blood count and urinalysis, including concentration tests, gave normal results. The Kahn reaction of the blood was negative. The serum calcium was 10.5 mg and the blood cholesterol 260 mg per hundred cubic centimeters. Roentgenograms revealed no evidence of osteitis deformans but did show calcification of blood vessels in his right thigh (fig 4 B). The electrocardiogram was normal. Permission for biopsy was refused.

Comment—In recapitulation, 2 patients with angioid streaks of the retina and pseudoxanthoma elasticum had unmistakable vascular changes in all the extremities. The changes, as far as could be determined, involved the peripheral arteries. Physical examination demonstrated complete absence of some and reduction in the amplitude of the remainder of the palpable pulses of the extremities. This was confirmed by oscillometric tracings, which demonstrated greatly diminished pulsation in the major arteries supplying the extremities. Such a decrease in pulsation can result from (1) obliteration of the proximal artery or (2) great expansion of the arterial bed, due to atonic smaller arteries, with consequent fall in pulse pressure. In the 2 cases described, the deficient oscillations, if due to partial or complete occlusion of the proximal arteries, suggested that a widespread collateral circulation had developed. The possibility of atonic smaller arteries as an explanation of the diminished pulsation could not be eliminated by this test alone. The normal central pulse pressure at the elbows, as determined with the sphygmomanometer, did give further evidence that the arterial pathways themselves were obstructed more peripherally.

Biopsy and subsequent pathologic study of the partially obstructed left ulnar artery in case 1 gave conclusive information as to the nature of the disturbance. During dissection of the ulnar vessels, while obtaining the specimen for biopsy, the tissues were found to be extremely vascularized by a highly developed anastomatic circulation. The ulnar artery was grossly thickened, with absence of normal pulsation. The lumen was nearly obliterated and contained little blood.

Pathologic Study—The pathologic sections of the vessels and skin of this patient were studied by Lieut Col James S Forrester and reported on as follows:

Artery A medium-sized, muscular artery was seen presenting a greatly thickened wall and great reduction of the lumen. The intima was relatively normal, the mural thickening being largely due to pronounced hyperplasia of the muscular coat. The bundles were somewhat disorganized. Weigert's stain for elastic tissue

showed a moderately heavy, normal internal elastic membrane. In the media, however, the elastic tissue was fragmented, and there was no continuity of the few swollen fibers seen. The media showed considerable vascularization. There was no inflammatory reaction and no thrombus. An associated vein showed little change except slight granularity and curling of elastic fibrils.



Fig 7 (case 1) —Photomicrograph of the skin

Skin The epidermis was not remarkable. The major change in the derma was swelling, granularity, vacuolation and fragmentation of the deeper elastic tissue (fig 7). This was spotty, being conspicuous in some areas and minimal in others. There was no inflammatory reaction. Increased basophilic staining of the basal layer of the epithelium was present.

Comment Both tissues showed, as a major change, extensive damage and disruption of the elastic tissue network. It may well be that the pronounced

muscular hypertrophy was a compensatory reaction to the loss of elastic tissue, support

Diagnosis—The diagnosis was elastic degeneration, muscular hyperplasia of the arteries and pseudoxanthoma elasticum

It seems reasonable to conclude, in view of the similar clinical pictures, that the disturbance in function of the peripheral arteries of the other patients was on the same pathologic basis and that this, in turn, was part of a general process of degeneration of elastic tissue throughout the body, causing also the angioid streaks of the retina and the pseudoxanthoma elasticum. The relationship to osteitis deformans mentioned in the literature, however, is by no means clear. Scholz, on the basis of the work by Ohno³ (1935) and Finnerud and Nomland³ (1937), whom he cited, suggested that there is a disturbance of calcium metabolism in patients with angioid streaks. These authors demonstrated calcium phosphate in the degenerative lesions. Scholz suggested that basophilic staining of Bruch's membrane might be associated with calcification. At any rate, in cases of osteitis deformans absorption and ossification of the involved bones occur simultaneously. Though in the cases reported here there were calcified peripheral vessels, no evidence of disordered calcium metabolism was found, although fractionation into diffusible and nondiffusible fractions was not made. Determinations of phosphatase could not be made.

The occurrence of pronounced arterial changes in 2 of 3 patients having angioid streaks of the retina and the mention of 1 patient with absence of palpable pulses in the lower extremities by Scholz suggest that the incidence of such a syndrome may be high if the cases previously reported in the literature could be reviewed with this in mind. The arterial changes may well explain, by shortened life expectancy, the sharp drop in the incidence of angioid streaks of the retina during the sixth and seventh decades of life. Emphasis is placed on careful ophthalmoscopic study of all patients with unexplained peripheral vascular disease because the clinical picture just described is probably more common than is now realized. Furthermore, there is no reason that the vascular condition might not dominate the picture, or even occur alone, as do angioid streaks of the retina and pseudoxanthoma elasticum in a significant number of cases.

SUMMARY

Three cases of angioid streaks of the retina are reported.

In 1 of these cases there was unexplained hypertension.

In 2 of these cases the angioid streaks were associated with pseudoxanthoma elasticum and diminution or absence of peripheral pulses.

Calcification of vessels in the thighs was demonstrated roentgenographically.

Pathologic study of a diseased ulnar artery in 1 case revealed degeneration of elastic tissue in the media with conspicuous hypertrophy of the muscularis and narrowing of the lumen, while study of the skin showed similar degeneration of elastic tissue

The angioid streaks of the retina, pseudoxanthoma elasticum and vascular disturbance reported in 2 cases were believed to be on the basis of a general degeneration of elastic tissue throughout the body and will probably be found to occur together not infrequently when such cases are studied with this in mind

Capt Graham Eddy and the First Medical Museum and Arts Detachment prepared the illustrations accompanying this paper

TESTS FOR THE DETECTION AND ANALYSIS OF COLOR BLINDNESS

III The Robkin Test

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IN A previous report¹ we discussed the general situation with respect to polychromatic test plates for the detection of defective color vision pointing out the advantages and limitations of this type of test and the need for care in administration. Stress was laid on the following four important sources of error which, aside from defects in the tests themselves, account for part of the failure of the tests to screen out all persons with defective color vision: (1) disregard of the critical importance of illumination, (2) careless and inefficient administration, (3) incompetent and invalid interpretation of results, (4) misapplication of the tests to fields for which they were not intended, or the expectation of more from the tests than they are capable of, or designed for, yielding

In that report a critical evaluation was made of the fifth edition of the Ishihara test for the analysis and detection of defective color vision. In a second report² the study was extended to include other representative editions of the Ishihara test. In these reports analysis was made (a) of each plate of the test as a medium for detecting defective color vision, (b) of the significance of performance scores on the entire test both for the detection of the presence of a defect in color vision and for the equally important classification of the type and extent of the defect, and (c) of the type of response to certain plates as a clue to classification.

In the present report a similar evaluation is made of Rabkin's "Polychromatic Plates for Testing Colour Vision." We find this test to be

From the Knapp Memorial Laboratories, Institute of Ophthalmology, Columbia University College of Physicians and Surgeons.

1 Hardy, L. H., Rand, G., and Rittler, M. C. Tests for Detection and Analysis of Color Blindness. I. An Evaluation of the Ishihara Test, *Arch. Ophth.* **34**:295-302 (Oct.) 1945.

2 Hardy, L. H., Rand, G., and Rittler, M. C. Tests for the Detection and Analysis of Color Blindness. II. A Comparison of Editions of the Ishihara Test. *Arch. Ophth.* **35**:109-119 (Feb.) 1946.

in many respects much more valuable and informative than the Ishihara test. It has equally good possibilities for screening persons with defective from those with normal color vision, in addition, when scored by the revised procedure to be described it yields, for 93 per cent of the subjects with defective red-green vision tested, correct information as to the nature of the red-green defect present. We do not find it adequate, however, to differentiate between dichromasy and anomalous trichromasy, as is claimed by Rabkin.

The Rabkin test was first published in 1936³. A second edition appeared in 1939⁴. The second edition does not differ from the first in general form. However, some of the pigments have been changed as the result of experimentation, and substitutions have been made for some of the plates. The test is distributed in this country by Four Continent Book Corporation, 253 Fifth Avenue, New York.

The Rabkin test is interesting in that it was designed to differentiate anomalous trichromasy from dichromasy and, at the same time, to furnish a differential diagnosis as to the type of dichromasy (protanopia, deutanopia, tritanopia), as well as to the type of anomalous trichromasy (protanomaly, deutanomaly). It is claimed, and, so far as we know, justly, that this is the first attempt to differentiate anomalous trichromasy from dichromasy by means of polychromatic printed plates. The subdivision of dichromasy into protanopia and deutanopia (1897)⁵ and tritanopia (1911),⁶ suggested by von Kries, and of trichromasy into normal and anomalous types, suggested by Nagel (1904),⁷ is followed by Rabkin. He does not, however, recognize the subdivision of blue-yellow blindness proposed by Muller (1924)⁸ into tritanopia (violet-yellowish green defect) and tetartanopia (blue-yellow defect). Rabkin defines tritanopia as "blue or violet colour-blindness". He states⁴:

3 Rabkin, E. B. *Polychromatic Plates for Color Sense Examination*, Kiev, State Medical Publishing Board, 1936.

4 Rabkin, E. B. *Polychromatic Plates for Testing Color Vision*, ed 2, Kiev, State Medical Publishing House, 1939.

5 von Kries, J. Ueber Farbensysteme, *Ztschr f Psychol u Physiol d Sinnesorg* **13** 241-324, 1897.

6 von Kries, J. Normale und anomale Farbensysteme, in von Helmholtz, H. *Handbuch der physiologischen Optik*, ed 3, Leipzig, L. Voss, 1911, vol 2, pp 333-347.

7 Nagel, W. A. Die Diagnose der anomalen trichromatischen Systeme, *Klin Monatsbl f Augenh* **42** 366-370, 1904.

8 Muller, G. E. Darstellung und Erklärung der verschiedenen Typen der Farbenblindheit nebst Erörterung der Funktion des Stäbchenapparates sowie des Farbensinns der Bienen und der Fische, Göttingen, Vandenhoe & Ruprecht, 1924.

In cases of tritanopia the spectrum is shortened at its violet end, the maximum of brightness is at the sodium line (line Na), and there are two achromatic zones—one in the blue colour, the other in the yellow colour regions

Theoretically, the method used by Rabkin in designing his plates was based on the fact of "different perception of the hues in the warm part of the spectrum for the normal trichromats and the dichromats and also on the differences of the brightness distributions in the spectrum for various colour systems" (page 31) ¹ That is, in planning plates designed to distinguish dichromasy from trichromasy he played mainly on the aspects of color confusion in the red-yellow-green region and on the presence of a neutral zone in the dichromatic spectrum, and in planning plates designed to distinguish deuteranopic and protanopic color vision he utilized chiefly the characteristic shift in the brightness of the colors and the different location of this neutral zone. For deuteranopia he locates the neutral zone in the green, at approximately 500 millimicrons, and for protanopia, in the blue-green, at approximately 490 millimicrons. He does not mention or utilize the second neutral region in the dichromatic color scheme (in the red-purple region for deuteranopia and in the red region for protanopia). This, we believe, is unfortunate, since it would have increased the value of some of the plates for differentiating between deuteranopia and protanopia. For the differentiation of anomalous trichromasy and dichromasy, he relies on the correct reading of certain specified plates.

The series comprises 20 plates, in most of which digits or simple geometric forms composed of colored disks varying in size, chroma and value (saturation and brightness) appear on backgrounds composed of colored disks similarly varying in size, chroma and value. In certain of the plates all of these variants are not used. Plates 1 and 2 are mainly for purposes of demonstration, plates 3 through 12 and plate 15 are intended for screening persons with defective color vision from persons with normal color vision, plates 13, 14, 16, 17 and 18 (in all of which more than one combination of figure and background appears) are used for differentiation of deuteranopia and protanopia, and plates 19 and 20, for the detection of tritanopia. The correct reading of one or several of plates 3, 4, 5, 6, 11, 16, 17 and 18 is the indication of anomalous trichromasy when the other plates are read in the same way as in cases of dichromasy. The type of anomaly (deuteranomaly or protanomaly) is determined by the occurrence of typical deuteranopic or protanopic responses or, in case a diagnostic plate is correctly read, by ascertaining which of the two digits or figures is seen more clearly. The instructions on this interpretation of the responses are rather detailed and require careful study to do justice to the diagnostic possibilities of the test.

Because the Rabkin test is not widely known or easily accessible, it may be worth while to describe some of the more unusual plates in detail. Plates 3, 4, 5, 9 and 11 are of the "transformation" type used by Ishihara, in which the subject with normal color vision sees one figure and the subject with defective color vision another. These plates are by no means a copy of the Ishihara plates, and the figure seen by the subject with defective color vision is much less visible to persons with normal color vision than it is in the Ishihara plates. Plates 6, 7, 8 and 10 are of "the vanishing pattern" type used by Stilling, Ishihara and others, in which the person with normal color vision sees a pattern and the person with defective color vision does not. In the Rabkin plates of this type the patterns vary as to visibility. The digit of plate 8, for example, is not seen by many persons of low normal color sensitivity. In plates 13, 14, 15, 16 and 17 different combinations of figure and background are ingeniously presented in various segments of the plate, some of which are seen by deuteranopic and some by protanopic subjects, some are transformation patterns and some are hidden figures not seen by subjects with normal color vision but visible to most persons with defective red-green vision. These are the plates chiefly used in classifying persons with deuteranopia and protanopia. A table of typical responses provides the key to diagnosis. Plate 18 is of particular interest as a test to differentiate between anomalous trichromasy and dichromasy. It consists of small red and green squares arranged on a gray background in a square formation so that there are 8 vertical arrays, numbered 1 to 8, and 8 horizontal arrays, numbered 9 to 16. Rows 9, 11, 13 and 14 consist of red squares, some darker than others, and rows 10, 12, 15 and 16 of green squares, some lighter and bluer than others. Columns 1, 2, 4, 6 and 8 contain the red and green squares of the same brightness, and columns 3, 5 and 7 contain the red and bluish green squares of unequal brightness. Instructions are to select those arrays which are one colored, although there may be variation in brightness. Subjects with normal color vision are supposed to select horizontal arrays 9 to 16, deuteranopic subjects, vertical arrays 1, 2, 4, 6 and 8, and protanopic subjects (who see red as darker and green as lighter than do persons with normal and deuteranopic color vision), vertical arrays 3, 5 and 7. Subjects with anomalous trichromasy are supposed to select either horizontal arrays alone or some horizontal and some vertical arrays. In case of the latter (mixed arrays) the defect in color vision is more extreme and the diagnosis of anomaly is cleancut, in case of the former (horizontal arrays only) the defect in color vision is less pronounced and the diagnosis that an anomaly is present is based on the failure to read certain other plates of the series.

Rabkin does not consider performance scores on the entire test, therefore he does not give any critical score to indicate the dividing line between low, but normal, color vision and defective color vision

EVALUATION OF THE SECOND EDITION OF THE RABKIN TEST
AS A MEANS OF DETECTING AND CLASSIFYING
DEFECTIVE COLOR VISION

The Rabkin test (second edition) was included as one test in a battery used in the Knapp Memorial Laboratories to study the persons with defective color vision referred to the laboratories. These subjects were not selected on the basis of any statistical survey. They included patients referred to us by ophthalmologists, men who had been rejected by the armed forces on the basis of defective color vision and subjects obtained from some of the New York city high schools, from Vanderbilt Clinic and from other sources. The battery included the following tests, which have been described in the literature

Ishihara Tests for Colour-Blindness (fifth edition)⁹

Rabkin Polychromatic Plates for Testing Colour Vision (second edition)⁴

Pseudo-Isochromatic Plates for Testing Color Perception, engraved and printed by Beck Engraving Co., Inc., and published and distributed by the American Optical Company¹⁰

Farnsworth-Munsell 100-Hue Test¹¹

Farnsworth Dichotomous Test¹¹

Inter-Society Color Council Single Judgment Test for Red-Green Discrimination¹²

Nagel Anomaloscope¹³

Several additional tests were used which have not as yet been described in print, notably a series of polychromatic plates and a new form of anomaloscope devised in this laboratory. The results of the entire battery of tests aided in the classification of the defective color vision as to type and extent. Our data thus permit us to evaluate each of the aforementioned tests as a screening medium and as a medium

9 Ishihara, S. Tests for Colour-Blindness, ed 5, Tokyo, Kanehara, 1925

10 Pseudo-Isochromatic Plates for Testing Color Perception, Southbridge, Mass., American Optical Company, Philadelphia, Beck Engraving Co., Inc., 1940

11 Farnsworth, D. The Farnsworth-Munsell 100-Hue and Dichotomous Tests for Color Vision, *J Optic Soc America* **33** 568-578, 1943

12 Hardy, L. H. A Single Judgment Test for Red-Green Discrimination, *J Optic Soc America* **33** 512-514, 1943

13 Nagel, W. A. Zwei Apparate für die augenärztliche Funktionsprüfung Adaptometer und kleines Spektralphotometer (Anomaloskop), *Ztschr f Augenh* **17** 201-222, 1907

for differential classification. The present paper, however, will be confined to the Rabkin test, mention being made of the battery of tests because of its use in classifying the subjects as to type and extent of the defect in color vision.

The classification of the subjects followed the scheme outlined by two of us¹⁴. To persons not familiar with the classic terminology of color blindness and those to whom this reference is not available, the following simple explanation of terms¹ may be of value.

On the Young-Helmholtz theory there are three factors in the color vision process: (1) The red primary, proto, or first, process, (2) the green primary, deuto, or second, process, and (3) the blue primary, trito, or third, process. Hence one should expect to find three types of color vision: (1) trichromatic, in which all three processes function, (2) dichromatic, in which only two processes function, and (3) monochromatic, in which there is only one differentiated physiologic process. Trichromatic color vision means that all three processes are functioning, but since one or more of the processes may function aberrantly there will be as a result three types of trichromatic color vision: (1) normal, (2) anomalous, in which one or more of the processes is weak, and (3) low discrimination in which apparently all processes are weak. Anomalous trichromasy is designated according to the process which is weak as (1) protanomaly, or predominantly red weak, (2) deuteranomaly, or predominantly green weak, and (3) tritanomaly, or predominantly blue-yellow weak. Dichromatic color vision means that only two of the processes are functioning and hence is similarly divided into three types: (1) protanopia, formerly called red blindness, (2) deuteranopia, formerly called green blindness, (3) tritanopia, formerly called blue-yellow blindness. As a mnemonic, we might point out that there are three kinds of abnormal color vision: (1) anomalous trichromasy (three types—protanomaly, deuteranomaly and tritanomaly), (2) dichromasy (also three types—protanopia, deuteranopia and tritanopia), and (3) monochromasy. Protanopia exhibits a shortened red end of the spectrum, a neutral area at about 493 millimicrons (in the blue-green), a second neutral band in the red (at 493 c) and a brightness peak which is shifted toward the violet. Deuteranopia shows a neutral region in the green (about 497 millimicrons), a second neutral band in the red-purple (at 497 c) and no shift in the luminosity peak. Tritanopia shows a shortened blue end of the spectrum and a neutral band in the yellow-green. The luminosity peak is not shifted. These types, as well as corresponding anomalous trichromatic types, are best detected and classified by anomaloscopic tests [298].

The subjects whose responses were used for the evaluation of the Rabkin test numbered 106. On the basis of their responses to the entire battery of tests, 74 were classified as subjects having defective color vision of the following types: Thirty-five had anomalous trichromasy, of whom 23 had the deuteranomalous and 12 the protanomalous form, 32 had dichromasy, of whom 15 had deuteranopia and 17 protanopia, and 7

14 Hardy, L. H., and Rand, G. Recent Developments in Color Vision Testing, Graduate Lecture, American Academy of Ophthalmology, Outlines of Instructional Courses, Continuous Course No. 6 and 7, 1944. Hardy, L. H., Rand, G., and Rittler, M. C. Color Vision and Recent Developments in Color Vision Testing, Arch. Ophth., to be published.

showed generally low color discrimination (that is, low discrimination of all colors) sufficient to amount to a defect in color vision. The remaining 32 subjects showed low color discrimination to a lesser degree which would not be sufficient to amount, in all probability, to a real defect in color vision. This last group we classified as having "low normal" color vision. In order to establish the presence of dichromasy and anomalous trichromasy, particular reliance had to be placed on the results obtained with the anomaloscope, the Farnsworth dichotomous test and our own polychromatic plates, and in order to establish the presence of low color discrimination and low normal color vision, on these tests and, in addition, on the Farnsworth-Munsell 100-Hue Test.

We recognize, of course, that the dividing line between the best of the group with low color discrimination and the worst of the group with low normal vision is arbitrary. The decision as to which group these borderline subjects belonged may perhaps be thought to have been intuitive on our part, but in the main it was based on various items in the composite picture such as (1) scores achieved on tests which yield quantitative scores, (2) types of error made (e.g., whether a digit on certain polychromatic tests was not seen at all or was merely read incorrectly sometimes because of carelessness, (3) comparative scores and types of error made on repetition of tests and (4) performance on color threshold, hue difference and color matching (color aptitude) tests, as well as responses made to questioning, etc. For example, all the subjects we have classified as having "low normal" color vision scored 75 or better on both the Ishihara (fifth edition) and the Rabkin test. The errors which were made were of the following nature: misreading a "13" for an "18", reading a "hidden digit," frequently incorrectly, or failing to see one of the digits of low visibility. In no case was more than one error made that could be considered of consequence. Further, in the cases in which these slight errors were made, responses to other important tests, such as the 100-Hue test, the dichotomous test, the anomaloscope or our polychromatic plates, were of the order considered within normal limits either by the author of the test or by us, as the result of experience.

For persons judged to have generally low color discrimination the picture was quite different. All scored less than 75 on both, the Ishihara and the Rabkin test, the errors made were of a more serious nature, and the responses to certain of the other tests, particularly the 100-Hue test, were not within the limits of normality established for the test.

Low intelligence and lack of interest and concentration obviously contributed to a poor performance on certain tests, particularly for some persons with low normal color vision. When such factors were present in a person with defective color vision, the performance score was

unquestionably lowered, but the presence of a real defect in color vision was evident in the type of response given

We feel confident that the subjects whose responses are used to evaluate the Rabkin test in this report and the Ishihara test in former reports¹⁵ are correctly classified in accordance with the scheme already outlined. We hope later to report typical individual performances exemplifying these types.

The subjects used in the present report, then, included persons with the following defects:

Type of Defect	No. of Subjects
Anomalous trichromasy	
Deuteranomaly	23
Protanomaly	12
Dichromasy	
Deuteranopia	15
Protanopia	17
Low color discrimination	7
All subjects with defective color vision	74
Subjects with low normal color vision	32

For all work with pigment test material a close approximation to I C I Illuminant C was used. The illumination on the test material was about 25 foot candles. The testing distance with the polychromatic test plates was about 30 inches (76 cm). Responses should be immediate (within two seconds). Hesitant or studied responses are viewed with suspicion. It should be mentioned also that in some of the Rabkin plates glossy pigments have been used. Special care must be taken, therefore, in the illumination of these plates and in the viewing angle to avoid specular reflection, which often affords a clue to either the correct or the incorrect response.

The results for the Rabkin test are summarized in tables 1 to 4. They will be discussed under four headings: (1) analysis of the individual plates, (2) significance of performance scores on the entire test, (3) differential classification of deuteranopia and protanopia, deuteranomaly and protanomaly, and (4) the differential classification of anomalous trichromasy and dichromasy.

ANALYSIS OF THE INDIVIDUAL PLATES

In table 1 is shown for each type of defective color vision and for low normal color vision the percentage of subjects who passed the individual Rabkin plates, designated by plate number. The first five horizontal rows of figures show these percentages for each type of defective color

¹⁵ Footnotes 1 and 2

TABLE 1—*Analysis of Individual Plates of the Rabkin Test (Second Edition)*

Type of Defective Color Vision	No of Sub- jects	Percentage of Subjects with Each Type Passing Individual Plates																	
		Plate No																	
		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Defective Color Vision	23	13	39	43	4	4	0	30	9	100	70	61	0	1	23	17	57	96	100
Anomalous trichromasy	12	8	92	0	0	8	0	0	0	75	33	0	0	0	8	0	83	92	100
Deutanomaly																			
Protanomaly																			
Dichromasy	15	0	0	27	0	0	0	0	0	100	60	7	0	0	0	0	7	100	100
Deutanopia	17	6	100	0	0	0	0	0	0	59	0	0	0	29	0	0	0	82	100
Protanopia																			
Low color discrimination	7	14	86	0	29	29	0	29	14	100	72	86	0	14	0	57	86	100	100
All subjects with defective color vision	74	8	53	19	4	5	0	12	4	86	46	28	0	9	8	11	50	93	100
Low normal color vision	32	94	100	78	100	94	44	100	91	100	97	100	91	100	100	94	100	97	100

vision and demonstrate the value of the individual plates for detecting each type. The bottom two rows present a comparison of the percentages for the subjects with defective color vision as a group and for the subjects with low normal vision as a group. This comparison shows the value of each plate as a diagnostic or screening medium. On the basis of this table the following points may be called to the attention:

1. Plates 6, 7, 8, 9, 10, 14, 16 and 17 were not passed by any of the subjects with dichromasy. (Of the plates which according to Rabkin are always failed by these subjects, plates 3, 4, 5, 11 and 18 are not included in this list.)¹⁶ Plates 8 and 14 were also not passed by any of the subjects with anomalous trichromasy or by any persons having low color discrimination, that is, these plates were not passed by any of our subjects having defective color vision. Plate 8, however, on which a faint reddish "5" is presented on a background of green lines, was passed by only 44 per cent of the subjects with low normal vision, but plate 14, which normal subjects read as "30" and subjects with dichromasy as either "16" or "106," was passed by 91 per cent of the subjects with low normal vision. Plate 14 is therefore, the best single screening test of the series.

2. Plates 4 and 11 are singled out for special discussion because we were not able to confirm Rabkin's report as to the response of the subject with defective color vision to these plates.

In plate 4 a triangle composed of red disks is presented on a background of green and blue disks. Superimposed on the triangle is a circle composed in part of red and in part of green disks. Normal subjects respond "triangle." According to Rabkin, both protanopic and deuteranopic subjects respond "circle." Among our observers all the deuteranopic and 61 per cent of the deuteranomalous subjects reported "circle" (i. e., failed). All the protanopic and 92 per cent of the protanomalous subjects, however, reported "triangle" (i. e., passed). They described the figure as a dark triangle on a lighter background. We believe that the brightness relationship between figure and background is so adjusted as to cause this plate to be passed by the protanopic subjects.

Plate 11 is in construction similar to plate 4, but in reverse color combination, that is, a triangle composed of green disks is presented on a background of red, orange and purple disks. Normal subjects respond "triangle." According to Rabkin, both protanopic and deu-

¹⁶ Rabkin⁴ stated (page 37) "The fundamental symptom, permitting to differentiate the anomalous trichromasy from dichromasy, is the correct reading of one or several of the plates 3, 4, 5, 6, 11, 16, 17 and 18 by the anomalous trichromats. Other plates are read by them in the same way as by dichromats."

teranopic subjects respond "circle." Among our observers all the deuteranalous and deuteranopic subjects reported "triangle"—the normal response, so also did 75 per cent of the protanalous and 59 per cent of the protanopic subjects. Of the remaining protanalous subjects, only 8 per cent reported "circle," and 17 per cent failed to see any pattern. Of the remaining protanopic subjects, only 18 per cent reported "circle," and 23 per cent failed to see any pattern. This plate, therefore, has no value as a test for red-green defect.

3 Plate 18 is the only one which shows a significant difference in the percentage of subjects with dichromasy and those with anomalous trichromasy who passed. Of the 32 subjects with dichromasy only 1 (3 per cent) passed this plate, but of the 35 subjects with anomalous trichromasy 30 (86 per cent) passed. The possibilities of this plate for classification as to protanopia and deuteranopia are discussed in connection with table 4.

TABLE 2—*Significance of Performance Score for Subjects Showing Each Type of Defective Color Vision and for Subjects with Low Normal Color Vision**

Type of Defective Color Vision	Number of Subjects	Average Score	Median Score	Range of Scores
Anomalous trichromasy				
Deuteranomaly	23	33	39	17-72
Protanomaly	12	28	25	17-39
Dichromasy				
Deuteranopia	15	22	22	17-28
Protanopia	17	21	22	11-33
Low color discrimination	7	45	50	17-72
All subjects with defective color vision	74	30	25	11-72
Low normal color vision	32	93	94	78-100

* The performance score is the percentage of the 18 plates to which perfect responses were given.

4 Plates 19 and 20, which were intended for the detection of the tritanopic type of defective color vision, were passed by most of the subjects with defective color vision tested. Plate 19 was passed by fewer of the protanopic type than of the deuteranopic type, and plate 20 was passed by all of both types. We have been able to test too few subjects having the tritanopic type of defect to give an opinion on the value of these plates for detecting such subjects.

SIGNIFICANCE OF PERFORMANCE SCORES ON ENTIRE TEST

Table 2 shows the performance scores obtained on the entire Rabkin test. In this table are given for each type of defective color vision and for low normal color vision (a) the average score achieved by each group of subjects, (b) the median, or middle, score for each group

and (c) the range of scores from lowest to highest achieved by the individuals within each group. A score of 100 indicates that correct responses were given to all 18 plates, a score of 0 means that no correct responses were given, and scores between 0 and 100 indicate the percentage of the 18 plates to which correct responses were given. As in table 1, the first five horizontal rows of figures give the data for each type of defective color vision and the bottom two rows the data for the subjects with defective color vision as a group and for those with low normal color vision as a group.

In table 2 it is seen (a) that the subjects with defective color vision as a group had an average performance score of 30 and the subjects with low normal vision an average score of 93, (b) that deuteranomalous subjects had an average score of 38 and deuteranopic subjects an average score of 22, and (c) that protanomalous subjects had an average score of 28 and protanopic subjects an average score of 21. On the basis of average performance scores, then, the Rabkin test would seem to separate persons with defective color vision from those with normal color vision and deuteranomalous from deuteranopic subjects. However, for the purposes of screening and classification, it is not the average score achieved by a group that is important, but the score achieved by the individual. This is shown in the last column of table 2, where for each type of defective color vision is given the range of scores, from lowest to highest, achieved by the subjects having that type of defect. This column shows clearly the overlapping of scores for the various types of defective color vision and thus demonstrates the impossibility of differentiating the type of defective color vision on the basis of the score alone. There is, however, no overlapping of scores between the group of subjects with defective color vision taken as a whole and the group with low normal color vision, the lowest score of the group with low normal vision being 78 and the highest score of the group with defective vision being 72. In round numbers, it would seem, then, that a critical score of 75 might be accepted as the dividing line between color-defective performance and normal performance on the Rabkin test.¹⁷

The overlapping of scores of subjects exhibiting the various types of defective color vision is brought out still more clearly in table 3, which shows the distribution of performance scores for each type. For representation in this table the following classes of performance scores

17 Of the subjects with defective color vision, only 3 per cent passed as many as 13 plates (score 72), 4 per cent passed 10 plates (score 56), and 9 per cent passed 9 plates (score 50). The remaining 84 per cent scored below 50.

Of the subjects with low normal color vision, only 3 per cent passed as few as 14 plates (score 78), 9 per cent passed 15 plates (score 83), 13 per cent passed 16 plates (score 89), 56 per cent passed 17 plates (score 94), and 19 per cent passed all 18 plates (score 100).

were made 0 to 6 (failure on all or all but 1 plate), 11 to 28 (passing 2 to 5 plates), 33 to 50 (passing 6 to 9 plates), 56 to 72 (passing 10 to 13 plates), 78 to 94 (passing 14 to 17 plates), and 100 (passing all plates). The overlapping of scores of subjects exhibiting the various types of defective color vision is clearly shown in this table, and, consequently, the inability of the Rabkin test to yield a classification as to either the type or the extent of the defect on the basis of the performance score.

TABLE 3—*Distribution of Performance Scores on Rabkin Test (Second Edition)*

Type of Defective Color Vision	Number of Subjects	Percentage of Each Group Achieving Scores of					
		0-6	11-28	33-50	56-72	78-94	100
		Number of Plates Passed					
		0 1	2 5	6 9	10 13	14 17	18
Anomalous trichromasy							
Deuteranomaly	23	0	30	57	13	0	0
Protanomaly	12	0	58	42	0	0	0
Dichromasy							
Deuteranopia	15	0	100	0	0	0	0
Protanopia	17	0	94	6	0	0	0
Low color discrimination	7	0	14	43	43	0	0
All subjects with defective color vision	74	0	62	30	8	0	0
Low normal color vision	32	0	0	0	0	81	19

The following points are brought out in tables 1, 2 and 3

1 The scores of subjects with anomalous trichromasy and of subjects having generally low color discrimination sufficient to amount to a real defect have a wider range of scatter than those of subjects with dichromasy (table 3). That is, as seems probable, their degree of defect may vary from a slight to an extreme anomaly or low discrimination, while subjects with dichromasy having defective red-green vision present a more homogeneous group, at least when studied by means of tests designed primarily to detect defective red-green vision.

2 All subjects with defective color vision of the red-green types, as well as subjects having low color discrimination amounting to a defect in color vision, are screened from subjects having normal and low normal color vision if a score of 75 is taken as the critical score in the Rabkin test (tables 2 and 3). In the group tested, no subject with defective color vision achieved a score of more than 72 and no subject with low normal vision a score of less than 78.

3 No cleancut separation as to either the extent or the type of the defect can be based on performance scores. While in general the subjects with dichromasy had lower scores than those with anomalous trichromasy, 30 per cent of the deuteranomalous and 58 per cent of protanomalous subjects had scores between 11 and 28, the range which

includes all but 1 of the subjects with dichromasy tested (table 3). Scores cannot, therefore, be used to indicate either the extent or the type of the defect in color vision.

4 Of the persons with dichromasy tested, all passed at least 1 of the 16 plates designed to detect deficiency in red-green vision (table 1). This is mainly due to the fact that none of the deuteranopic subjects failed plate 11 and none of the protanopic subjects failed plate 4. A score of 22 is both the median and the most frequent score for persons with dichromasy (table 2).

DIFFERENTIAL CLASSIFICATION OF DEUTERANOPIA AND PROTANOPIA, DEUTERANOMALY AND PROTANOMALY

So far we have discussed performance scores on the Rabkin test both as a means of detecting the presence of a defect in color vision and as a means of classifying the type of defect and have shown that the score achieved is adequate to distinguish defective from normal color vision when the test is properly administered but is not adequate to make the equally important classification as to the type and the extent of the

TABLE 4—*Key to Diagnosis on Basis of Type of Response*

Plate No	Reading of Plates		
	Normal Trichromats	Deuteranopes	Protanopes
12	12	12	
13	ct	ct	c
14	30	16	106
16	96	6	9
17	tc	c	t
18	9-16	1, 2, 4, 6, 8	3, 5, 7

defect. It remains to discuss the type of response to certain plates as a clue to this classification. Since this classification constitutes a unique and important feature of the Rabkin test, the individual plates designed to indicate the type of deficiency in red-green vision, as well as the test as a whole, will be discussed from that point of view.

Rabkin uses different series of plates to classify the type of defect in red-green vision among persons with dichromasy and those with anomalous trichromasy.

Dichromasy—According to Rabkin, deuteranopic and protanopic subjects give a differential response to plates 12, 13, 14, 16, 17 and 18. His key to diagnosis (classification) on the basis of type of response is given in the table above (table 4). In practice, however, the following are some of the difficulties that are encountered in interpreting responses actually given to these plates by subjects with color-defective vision.

Plate 12 Of our deuteranopic subjects, 60 per cent read "12", 7 per cent read the digit incorrectly, and 33 per cent failed to see the digit. Of our protanopic subjects, 88 per cent failed to see the digit, and 12 per cent read it incorrectly. We feel that this type of plate yields ambiguous results, for the following reasons: (a) The correct response can indicate either normal or deuteranopic vision, while failure to see the digit may be due either to a protanopic type of defect or to too low a color sensitivity to perceive the pattern (33 per cent of persons with deuteranopia, as well as 28 per cent of subjects having low discrimination, failed to see any pattern), and (b) it is impossible to interpret an incorrect reading of the digit.

Plate 13 Here, again, according to Rabkin, persons with normal trichromatic vision and those with deuteranopia give the same response. In this case both types see "circle and triangle," while protanopic subjects see only "circle." Of our deuteranopic subjects, however, only 7 per cent reported seeing "circle and triangle" (normal and deuteranopic response), 80 per cent saw "triangle" (ambiguous response), and 13 per cent saw no pattern (ambiguous response). Of our protanopic subjects, all saw "circle" (typical response for a protanope). For this plate we are unable to confirm Rabkin's schema.

Plate 14 According to Rabkin, persons with normal trichromatic vision read "30," deuteranopic subjects "16" and protanopic subjects "106." The "3" and the "1" of this plate form a transformation pattern, the "0" is intended to be a vanishing digit for deuteranopic subjects, and the "6" is a hidden digit supposedly seen only by persons with defective color vision. Of our deuteranopic subjects, only 60 per cent read "16." The remaining subjects failed to see either the "6" or the "1" or else gave incorrect readings that could not be interpreted. Of our protanopic subjects, only 41 per cent read "106", 24 per cent read "16" (the deuteranopic response), and the remainder either failed to see any digits or read them incorrectly. A greater variety of responses was given to this plate than to any other in the test. This plate, therefore, has slight, if any, value.

Plate 16 According to Rabkin, subjects with normal trichromatic vision read "96," deuteranopic persons "6" and protanopic persons "9." In evaluating the response given to this plate and to plate 17, we amplified Rabkin's procedure as follows. If the classifying digit was read correctly and the other digit incorrectly, the correct reading was accepted as furnishing the clue to classification. For example, "56" was accepted as diagnostic of deuteranopia, and "95," as diagnostic of protanopia. On this basis, all our deuteranopic and 71 per cent of our protanopic subjects were correctly typed. The remaining protanopic subjects either saw no digits at all or read the classifying digit incorrectly.

Plate 17 According to Rabkin, persons with normal trichromatic vision see "triangle and circle," deuteranopic subjects see "circle" and protanopic subjects see "triangle." Of our deuteranopic subjects, 93 per cent were correctly typed by this plate, and of our protanopic subjects, 82 per cent. The subjects who were not typed either saw no pattern or read it incorrectly.

Plate 18 According to Rabkin, persons with normal trichromatic vision see as one colored the horizontal arrays 9 to 16, deuteranopic subjects, the vertical arrays 1, 2, 4, 6 and 8, and protanopic subjects, the vertical arrays 3, 5 and 7. In evaluating our responses to this plate, we accepted as diagnostic of deuteranopia or protanopia the selection of any one of the designated vertical arrays so long as no horizontal arrays were also selected. Even with this favorable interpretation, only 40 per cent of our deuteranopic and 59 per cent of our protanopic subjects were correctly typed. Of the remaining deuteranopic subjects, 20 per cent saw only horizontal arrays as one colored (the normal response), 27 per cent reported as one colored some horizontal arrays and some of the vertical arrays 1, 2, 4, 6 and 8 (deuteranomalous response), and 13 per cent, some horizontal arrays and some of the vertical arrays 3, 5 and 7 (protanomalous response). Of the remaining protanopic subjects, 35 per cent reported as one colored some horizontal arrays and some of the vertical arrays 3, 5 and 7 (protanomalous response), and 6 per cent saw all the arrays, both horizontal and vertical, as one colored (ambiguous).

In order to give the most favorable interpretation to the value of the Rabkin test as a whole for differentiating between deuteranopic and protanopic dichromasy, we selected plates 16 and 17 as eliciting the fewest ambiguous responses and as "typing" the greatest number of subjects correctly. For a successful diagnosis we used the following criteria: 1. A subject was called classified as to type of defect by the plate in question when one pattern was read correctly and the other was not seen at all or was read incorrectly. 2. A subject was called classified as to type of defect by the test as a whole when a correct typing was obtained on either plate 16 or plate 17. By these criteria, all of our deuteranopic and 94 per cent of our protanopic subjects were correctly classified as to type of defect in red-green vision. The 1 subject who was not typed failed to see a pattern on either plate. It may be added that the only plate on Rabkin's list that might have typed this subject was plate 12, on which, again, he saw no pattern. Since 33 per cent of our deuteranopic subjects also failed to see a pattern on plate 12, this failure to respond could scarcely be called a clue to diagnosis.

Anomalous Trichromasy—To differentiate the type of defect in red-green vision among subjects with anomalous trichromasy, Rabkin employs plates 13, 16 and 17.

Plate 13 This plate is inadequate for this detection among subjects with anomalous trichromasy, for the same reason as it is inadequate among persons with dichromasy. Of our deuteranomalous subjects, 61 per cent reported "circle" and "triangle" (the normal and the deuteranopic response, according to Rabkin), 13 per cent saw "triangle" (an unclassified response), 13 per cent saw "circle" (the protanopic response), and 13 per cent failed to see a pattern. All our protanomalous subjects, however, reported "triangle."

Plate 16 By this plate 74 per cent of our deuteranomalous and 83 per cent of our protanomalous subjects were correctly classified. The remainder read either both digits or neither digit correctly, that is, they gave ambiguous responses.

Plate 17 By this plate 70 per cent of our deuteranomalous and 92 per cent of our protanomalous subjects were correctly classified.

TABLE 5—*Differential Classification of Deuteranopia and Protanopia, Deuteranomaly and Protanomaly**

Type of Defective Color Vision	No of Sub jects	Percentage of Subjects Correctly Classified by				Percentage of Subjects Incorrectly Classified by				Percentage of Subjects Not Classified by			
		Plate		Both Plates	Either Plate	Plate		Both Plates	Either Plate	Plate		Both Plates	Either Plate
		16	17			16	17			16	17		
Anomalous trichromasy													
Deuteranomaly	23	74	70	52	83	0	0	0	0	26	30	48	17
Protanomaly	12	83	92	75	100	0	0	0	0	17	8	25	0
Dichromasy													
Deuteranopia	15	100	93	93	100	0	0	0	0	0	7	7	0
Protanopia	17	71	82	65	94	0	0	0	0	29	18	35	6

* Analysis of the value of plates 16 and 17 as a means of differentiating between deuteranopic and protanopic types of subjects with defective red-green vision.

As in plate 16, the remainder saw correctly either both patterns or neither pattern (ambiguous responses).

Applying the two criteria for a successful diagnosis by the test as a whole, which was discussed in the section on "Dichromasy," we find that 83 per cent of our deuteranomalous and all our protanomalous subjects were correctly classified, none were incorrectly classified and 17 per cent of the deuteranomalous subjects were not classified. Had plate 13 been included among the diagnostic plates, as was done by Rabkin, 13 per cent of the deuteranomalous subjects would still have been unclassified, and 4 per cent would have been incorrectly classified as protanomalous.

It should be added that Rabkin suggests one further clue to the detection of the type of defect in red-green vision in those subjects with anomalous trichromasy who read both patterns correctly—that they be asked to designate which pattern is "plainer" or "clearer." We have found this

procedure most unsatisfactory, because the figure supposed to be seen more clearly by the deuteranomalous type is also seen more clearly by subjects of normal color vision. This designation can, then, hardly be called evidence of deuteranomaly.

The results obtained from plates 16 and 17 and from the test as a whole by the interpretation outlined are summarized in table 5.

Our conclusion is that when the results are evaluated in the revised manner described the Rabkin test affords an excellent, but not entirely perfect, medium for the differential classification of the type of defect in red-green vision not only among persons with dichromasy but among those with anomalous trichromasy.

DIFFERENTIAL CLASSIFICATION OF ANOMALOUS TRICHROMASY AND DICHROMASY

Rabkin is the first, so far as we know, to claim to be able to differentiate between anomalous trichromasy and dichromasy by means of polychromatic plates. It is of interest, therefore, to compare the results obtained by his method with those obtained with the Nagel Anomaloscope, on the basis of which this differentiation was originally proposed and the classification of our subjects is largely established.

Rabkin's method is summed up in this statement ⁴

The fundamental symptom permitting to differentiate the anomalous trichromasy from dichromasy is the correct reading of one or several of the plates 3, 4, 5, 6, 11, 16, 17 and 18 by the anomalous trichromats. Other plates are read by them in the same way as by dichromats.

He lays special emphasis on the reading of plate 18. According to him, protanopic subjects see as one colored columns 3, 5 and 7, deuteranopic subjects, columns 1, 2, 4, 6 and 8, persons with anomalous trichromasy with a high degree of defect approaching dichromasy see some horizontal and some vertical arrays as one colored, and persons with anomalous trichromasy with a low degree of defect approaching normal trichromasy see only the horizontal arrays as one colored. The defect in the last-mentioned group is detected by the failure of the subjects to read correctly other plates of the test.

According to our results, Rabkin's method is not adequate to differentiate between anomalous trichromasy and dichromasy. All our subjects with anomalous trichromasy were classified as such by his procedure in that they read correctly one or more of the plates he listed, failed on several of the remaining plates and in plate 18 saw as one colored either horizontal arrays alone (87 per cent of the deuteranomalous and 83 per cent of the protanomalous subjects) or some horizontal and some vertical arrays (13 per cent of the deuteranomalous and 17 per cent of the protanomalous subjects). These subjects were, then, correctly classified by Rabkin's criteria.

However, by his first criterion, all our subjects with dichromasy are also classified as having anomalous trichromasy. It will be remembered from the section on "Analysis of the Individual Plates" that all our deuteranopic subjects passed plate 11 and all our protanopic subjects passed plate 4. Further, 33 per cent of our deuteranopic and 41 per cent of our protanopic subjects passed 1 or more other plates in the critical list. All our subjects with dichromasy, then, read correctly at least 1, and 38 per cent read 2 or more, of the specified plates. His second criterion (i.e., the response to plate 18) is also inadequate to separate subjects with dichromasy from those with anomalous trichromasy. By it only 40 per cent of our deuteranopic and 59 per cent of our protanopic subjects are classified as having dichromasy. In brief, a total of only 50 per cent of our subjects with dichromasy are correctly classified as such by his second criterion, and none are so classified by his first criterion.

COMMENT

There are two ways in which the possibilities of the Rabkin test for the differential classification of the type and the degree of the defect could be improved.

1 *In the Pigments Used*—Rabkin makes no use of the second neutral range in the color scheme of deuteranopic as compared with that of protanopic persons, i.e., in the red-purple region for the former and in the red region for the latter. This would have been especially useful in plate 18. The vertical arrays supposed to be seen as one colored by deuteranopic subjects would then have consisted of squares of red-purple and green of the same brightness, instead of red and green, those supposed to be seen as one colored by protanopic subjects, of squares of lighter red and darker blue-green. The expectation that characteristic vertical arrays would be selected as one colored would thus be increased and, since horizontal arrays would clearly appear to dichromatic subjects as squares of blue, yellow and gray, the expectation that horizontal arrays would be selected would be decreased.

2 *In the Chroma of Pigments Used*—It is logical that lower chroma pigments are needed to detect the type of defect in those subjects whose defect is less pronounced and higher chroma pigments are needed for this detection in those whose defect is extreme. The use of similar type plates in a series of graded chromas would aid also in the determination of the degree or extent of the defect. We have made plates somewhat similar to Rabkin's plate 18 involving both these features. On preliminary trial, these plates seem adequate for the dual differentiation, i.e., the separation of anomalous trichromasy from dichromasy and the classification within each group of the type and degree of defect in red-green vision. This work will be reported on later.

CONCLUSIONS

Used with care in administration, scoring and interpretation, the Rabkin test yields much more information concerning the type of defect of the examinee than does, for example, the Ishihara test or the American Optical Company test. As the result of our study of the test, changes in scoring certain of the plates are recommended, a revised procedure for classifying the type of defect in red-green vision is described, and constructive comments are offered for the improvement of some of the plates. In addition, the following general conclusions concerning the second edition of the Rabkin test seem justified:

- 1 Properly administered, the test affords a good device for screening the subject with defective color vision from the subject with normal color vision if 75 is taken as the critical performance score.

- 2 No analysis as to type or extent of defect can be based on the score alone.

- 3 The test taken as a whole affords an excellent means of classifying red-green dichromasy into the two groups protanopia and deuteranopia, and of classifying red-green anomalous trichromasy into the two groups deuteranomaly and protanomaly.

- 4 The test as now constructed is, however, not adequate to differentiate anomalous trichromasy and dichromasy.

To clarify 3 and 4, the conclusions might be stated in this manner: If one designates both dichromasy and anomalous trichromasy as either "proto" (predominantly red-defective) or "deutero" (predominantly green-defective), and if one further designates anomalous trichromasy as "ous" and dichromasy as "opic," then the Rabkin test effectively aids in differentiating the "proto" from the "deutero" type but is inefficient in separating the "ous" from the "opic" form.

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HYPERPYREXIA IN TREATMENT OF OCULAR CONDITIONS DUE TO SYPHILIS

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The induction of fever has been used by ophthalmologists in the treatment of various ocular conditions for many years. According to Cordes,¹ the usual methods of fever therapy applicable to ophthalmology include

- 1 Parenteral and intramuscular injections of foreign proteins
 - A Native proteins (milk)
 - (1) Caseins (Yatren-Casein, Caseosan, Alobintin, Perprotasin and Aolan)
 - (2) Egg albumin
 - B Protein split products (peptone-albumose, proteoses, pepsin)
 - C Tissue extracts (bovine uveal pigment)
 - D Serums (serums of Roux and Behring, Deutschmann's yeast serum, auto serum, normal horse serum and antitoxins)
 - E Vaccines—mainly typhoid
 - F Typhoid antigen
 - G Bacterial extracts (Coley's mixed toxins, Omnadin)
- 2 Malarial therapy
- 3 Physical means
 - A High frequency methods
 - (1) Diathermy
 - (2) Radiothermy (short wave)
 - (3) Inductothermy
 - B Kettering Hypertherm

¹ Cordes, F C Fever Therapy in Ophthalmology, J A M A **124** 14-23 (Jan 1) 1944

To these Castleden² would add the external production of heat (by hot water baths, steam baths and blanketing) and the use of drugs (such as injections of sulfur or tetrahydrobetanaphthylamine)

The beneficial results observed clinically in response to properly controlled fever therapy have been attributed to many physiologic responses of the body: the increase in the basal metabolism³, the decrease in the potency of the bacterial toxins due to an increased serum level of certain proteolytic enzymes⁴, the decrease in the circulation time of the blood, with resultant increased supply of fresh blood to the vascular bed of the eye⁵ and more rapid dilution and removal of the products of locally diseased tissues, leukocytosis and an increase of phagocytosis,⁶ and, in many cases, definite bacteriostasis due to heat and a higher antibody content of the blood stream, with a similar increase in the aqueous humor. To these must be added the fact that many ocular conditions show most of their pathologic changes in or adjacent to the uveal tract, a highly vascularized bed, in which there must appear a huge amount of capillary dilatation in the presence of prolonged elevation of temperature⁶.

Syphilis is the cause of some of the most intractable diseases of the eye, many of which lead ultimately to partial or complete blindness. Therefore it is felt that the experiences at a Marine hospital in the use of artificial fever in the treatment of syphilitic diseases of the eyes would be of interest.

METHOD

We have been using the Kettering Hypertherm for the treatment of syphilitic ocular conditions, after the method previously described by Trautman⁷, Knight, Emory and Callahan⁸ and Hall⁹. The accepted contraindications to treatment are observed,¹⁰ and each patient's cardiac, renal and pulmonary status is closely evalu-

2 Castleden, L. I. M. The Use of Artificial Pyrexia in the Treatment of Disease, *Practitioner* **140** 285-292 (March) 1938

3 Hench, P. S. Clinical Notes on the Results of Fever Therapy in Different Diseases, *Proc. Staff Meet., Mayo Clin.* **10** 202-207 (March 27) 1935

4 Petersen, W. F. Protein Therapy and Nonspecific Resistance, New York, The Macmillan Company, 1922

5 Berris, J. M., and Newman, M. N. Fever Therapy in Ocular Diseases, *Arch. Phys. Therapy* **19** 615-618 (Oct.) 1938

6 Sanders, T. E. Nonspecific Protein Therapy in Ocular Disease, *J. Iowa M. Soc.* **31** 51-52 (Feb.) 1941

7 Trautman, J. A. Hyperpyrexia. The Indication and Complications, with an Evaluation of Results Based on 5,500 Fever Sessions, New Orleans *M. & S. J.* **92** 630-637 (May) 1940

8 Knight, H. C., Emory, M., and Callahan, N. Hyperpyrexia in the Treatment of Acute Ocular Inflammations, *Am. J. Ophth.* **27** 381-388 (April) 1944

9 Hall, L. T. The Present Status of Fever Therapy, *J. Iowa M. Soc.* **28** 599-608 (Dec.) 1938

ated before each treatment is administered. Special nurses are employed, and the pulse, rectal temperature, blood pressure and respiratory rate are closely watched, each being checked at least every half-hour from the very beginning of the induction of fever until the temperature has finally returned to normal levels. Urinalyses are made before and after each treatment. Adequate intake of fluids is insured by parenteral injection of dextrose and saline solutions throughout the treatment, and a mixture of oxygen and carbon dioxide is administered frequently during the treatment to combat the decrease in the amount of these gases in the blood. It has been found that the patients are most easily managed throughout the treatments with the aid of liberal doses of hypnotics (Pantopon [a mixture of the hydrochlorides of the opium alkaloids] and scopolamine). Treatments are generally five hours in duration, at a temperature range of 104.5 to 105.5 F. The frequency with which they are administered varies from once a day to once in seven to ten days. The duration of each treatment, the interval between treatments and the total hours of treatment administered are individualized, the department of ophthalmology working in cooperation with the department of fever therapy in an effort to determine the amount of treatment which may be used safely to obtain clinical improvement or arrest. Each patient is regularly examined by the attending syphilologist, who recommends and administers whatever form of antisyphilitic chemotherapy he may deem advisable for the patient in question.

TABLE 1—*Atrophy of the Optic Nerve*

Case No	Name	Age	Total Hours of Treatment	No of Treatments	Temperature Range, F	Condition Improved	Condition Arrested	No Effect or Condition Worse
1	G A	50	20	4	104-105	Yes		
2	O N	55	15	3*	104-106		Yes	
3	W A	54	100	20	105-106		Yes	
4	T O	31	5	1†	104-106		(See text)	
5	J R.	45	55	11	104-105		Yes	
6	A A	36	74	24	104-106	Yes		
7	J G	34	100	20	105-106		Yes	
8	F A	38	85	17	105-106	Yes		
9	W B	48	50	10	105-106		Yes	
10	J P	47	50	10	105-106		Yes	
11	R A	46	25	8	105-106		(See text)	
12	L P	35	82	21	105-106			Yes
13	S B	46	85	22	105-106		Yes	
14	O B	34	38½	12	105-106			Yes
15	M P	31	50	5	105-106			Yes
16	H M	45	50½	10	105-106			Yes
17	E P	49	39	8	102-105	Yes		
18	H H	?	46	9	104-106			Yes
19	I C	45	50	10	105-106			Yes
Summary						4	7	6

* Patient also received nine "typhoid drips"

† Patient also received ten "typhoid drips"

ATROPHY OF OPTIC NERVE

The results of treatment in the cases of this condition are given in table 1. In all cases adequate antisyphilitic chemotherapy was given, in addition to the fever treatment indicated in the table.

10 Wallace, J, and Bushby, S R M. Hazards of Hypertherm Treatment, *Lancet* 2 459-464 (Oct 7) 1944. Culler, A M and Simpson, N M. Artificial Fever Therapy in Cases of Ocular Syphilis, *Arch Ophth* 15:624-644 (April) 1936. Sanders.⁶

By "arrested," in table 1, is meant cessation of progression of symptoms or a notable reduction in the rapidity with which the disease was progressing prior to the institution of the fever therapy, so that some effective vision remained

In this group there were 19 cases. It is interesting to note that in all the cases in this series, with the exception of case 9, there was binocular involvement. In 3 of these cases syphilitic ocular conditions other than atrophy of the optic nerve were present. In case 9 there was atrophy of the nerve in the right eye only, with disseminated chorioretinitis in the same eye and central choroiditis in the left eye. Treatment had no effect on the visual acuity (right eye, blind, left eye, 20/25) or the visual fields. In case 17 there were residual old, quiescent changes, indicating uveitis of long standing. It is of interest to note that fever treatment failed to improve the patient's vision but did effect a great enlargement of his visual fields. In case 19 intensive fever therapy and chemotherapy were given for severe exudative choroiditis. At the time of the initial examination it was noted that the disks were normal. The choroiditis improved greatly with the first two treatments but bilateral atrophy of the optic nerve set in during therapy. This was observed in 1 other case. In case 12 bilateral atrophy of the optic nerve developed while the patient was receiving intensive therapy, and rapidly progressing diminution of vision ensued. Fever treatments were being employed in this case for syphilis of the central nervous system.

Case 11 is included in the series despite that fact that complete blindness had been present one month before treatment was instituted. In case 17 it is believed that the great enlargement of the previously greatly constricted peripheral fields indicated improvement in the disease process involving the nerve and that the failure of visual acuity to improve was due to the old chorioretinal changes.

Of the cases listed as those in which "improvement" occurred definite pallor of the disks and marked constriction of the peripheral fields were present in case 1, although vision was still 20/20 in each eye. At the end of the course of therapy, vision was 20/15 in each eye, and there was a notable increase in the size of the peripheral fields. No relapse has been reported to date (two years later). In case 6 vision was limited to motions of the hands in the right eye and was 20/50 in the left eye, with a history of progressive, gradual loss of vision over a period of seven years. Vision in the right eye improved to ability to count fingers at 4 feet (120 cm), vision in the left eye remaining unchanged, with no relapse reported to date (two and one-half years later). In case 8 there was poor light projection in each eye, and this was improved with treatment to a point at which the patient was able to count fingers accurately at 3 feet (90 cm). In case 17, previously

described, an increase occurred in the extent of the peripheral fields, which has remained unchanged for six years. Because of this, the case is also listed as one in which improvement resulted.

It will be noted that in 2 cases (2 and 4) the "typhoid drip" technic was used to induce fever, in addition to the Hypertherm. Therapeutic fever was attained and maintained in a manner comparable to the Hypertherm method with the technic described by Knight, Emory and Flint.¹¹ This method consists in administration of massive doses of triple typhoid vaccine slowly by intravenous infusion and is a satisfactory substitute for use of the Hypertherm in attaining therapeutic fever. It has not been shown to have any advantages over the Hypertherm method which is believed to be safer, more efficacious and less uncomfortable to the patient.

Of the 19 cases of atrophy of the optic nerve in which this method was employed, improvement resulted in 4, or 21 per cent, arrest of clinical progression of symptoms was obtained in 7, or 37 per cent and in 6 cases, or 32 per cent, either there was no improvement or arrest or the onset actually seemed to have occurred during therapy. Cases 4 and 11, although included in the total number, are not placed in either of these categories. In case 4 some improvement occurred in the one eye, and definite progression of the disease took place in the fellow eye, and in case 11 the patient was totally blind one month before any treatment was instituted.

In all the cases listed in table 1 the patients were observed over a period of at least two years.

SYPHILITIC CHOROIDITIS

Six patients were treated with the Kettering Hypertherm for syphilitic choroiditis or chorioretinitis. The results obtained with this treatment are shown in table 2. Here results were much more spectacular. In 4 of the 6 cases reported, or in 67 per cent, pronounced and rapid improvement occurred. These were mainly cases of exudative choroiditis, in a more or less active or acute stage. In both the cases in which the Hypertherm treatment was without effect old, quiescent lesions were present. Brief summaries of illustrative cases follow.

CASE 27—A 30 year old white merchant seaman received intensive antisyphilitic chemotherapy and malarial therapy for syphilis of the central nervous system and then had forty-one and a half hours of fever treatment, with temperatures ranging from 104 to 106 F, in nine divided doses. Vision before the Hypertherm treatment was instituted was 20/200 in the right eye and 20/40 in the left eye.

11 Knight, H. C., Emory, M. L., and Flint, L. D. A Method of Inducing Therapeutic Fever with Typhoid Vaccine Using the Intravenous Drip Technic, *Ven. Dis. Inform.* 24:323-329 (Nov.) 1943.

Extensive disseminated chorioretinitis was present in the right eye, and the left eye showed a large patch of choroiditis. Because of the apparent quiescence of these lesions (a diagnosis based on the history and results of ophthalmoscopic examination) and the long antecedent history, it was not believed that any therapy would be of aid in the ocular condition. All treatment was directed toward involvement of the central nervous system. Because of slight visual improvement apparent after the first course of fever therapy, he was given an additional fifty hours, in ten doses. His vision improved to 20/160 in the right eye and to 20/20—1 in the left eye, and there was a striking reduction in the size of all scotomas.

CASE 32—A 45 year old Negro was admitted with vision of 20/160 in the left eye. Severe syphilitic uveitis with secondary glaucoma was present. The accepted local ocular therapeutic measures were employed, and he received forty-two hours of Hypertherm treatment, in eleven sessions. The ocular tension was reduced to within normal limits after the second treatment, and final vision in the left eye was 20/30.

TABLE 2—*Syphilitic Choroiditis*

Case No.	Name	Age	Diagnosis	Total Hours of Treatment	No of Treatments	Temperature Range, F	Results
20	I O	45	Exudative choroiditis	50	5	104-106	Choroiditis improved, optic nerve atrophy set in
21	W B	48	Old disseminated chorio retinitis	30	10	105-106	Treatment for optic nerve atrophy, no change
22	E P	49	Residue of old uveitis	30	5	102-105	Treatment for optic nerve atrophy, improvement
27	J F	30	Extensive disseminated chorioretinitis, O D, patch choroiditis, O S	91½	19	105-106	Marked improvement
32	G A	45	Acute exudative choroiditis	42½	11	105-106	Marked improvement
36	O T	30	Acute exudative choroiditis	30	3	105-106	Marked improvement

SYPHILITIC IRITIS

There were 6 cases in this group. Here, also, the results were excellent. It has been claimed by many authorities that the iritis commonly found in patients with secondary syphilis need not be treated with anything other than the usual local methods of medication and antisyphilitic chemotherapy. Our experience leads us to believe that, while this may be true, a more rapid response is to be obtained with the simultaneous use of the Kettering Hypertherm. The relief from pain is so prompt as to constitute in itself a cardinal reason for its use. In table 3 are given the data on 6 cases in which this treatment was used.

Because the results here were uniformly so good and because it is believed that the form of therapy herein described is particularly useful with this condition, brief résumés of all 6 cases follow.

CASE 23—The patient was admitted with secondary syphilis and a typical picture of acute plastic iritis of the left eye. Vision was 20/80 in this eye. He was given instillations of atropine and one treatment of five hours at 105 to 106 F in the Hypertherm, and there was almost complete resorption of the lesion from this single treatment. Instillation of atropine was continued for three weeks, and vision was then 20/20.

CASE 24—The patient presented a picture identical with that in the preceding case, and vision in the left eye was 20/120. He received twenty hours of treatment in the Hypertherm, in four sessions, and there was complete clearance of the lesions in twelve days, with resultant vision of 20/20.

CASE 25—Here, again, a picture similar to that in cases 23 and 24 was presented. Vision in the affected eye was 20/50 on the patient's admission. Treatment consisted of fifteen hours in the Hypertherm, in three doses, in addition to the usual local therapy with atropine. The iritis had appeared during a "rest period" after

TABLE 3—*Syphilitic Iritis*

Case No	Name	Age	Diagnosis	Total Hours of Treatment	No of Treatments	Temperature Range, F	Results
23	J H	37	Secondary syphilis and acute iritis	5	1	105-106	Almost complete resorption of iritis with one treatment
24	W G	28	Secondary syphilis and acute iritis	20	4	105-106	Decided improvement with one treatment, complete clearance in 12 days
25	T M	21	Secondary syphilis and acute iritis	15	3	105-106	See case report
26	T S	41	Iridocyclitis *	20	2	105-106	See case report
34	A C	43	Iritis	23	5	105-106	See case report
37	R H	27	Secondary syphilis and iritis	20	4	105-106	See case report

* With secondary glaucoma (also basal iridectomy)

the first part of the antisyphilitic chemotherapy had been completed. There was immediate improvement after his first Hypertherm treatment, and four weeks later vision was 20/20 in the affected eye.

CASE 26—A 41 year old Negro was admitted with severe exudative iridocyclitis, seclusio pupillae and secondary glaucoma, on a syphilitic basis. The condition had appeared two weeks prior to the date of his admission, while he was at sea and no treatment was available. A basal iridectomy, with surgical freeing of the posterior synechias, was done on the day of his admission, and he was then given twenty hours of Hypertherm treatment, in two doses. Vision on his admission was limited to light projection. There was decided improvement with his first treatment, and final vision was 20/160.

CASE 34—A 43 year old seaman was admitted with severe ulcerative keratitis and iridocyclitis in the left eye, with vision of 20/200 in that eye. This strange stoic gave a history of having had this condition for ten weeks previous to his admission, during which time he had received no treatment. Whether or not his negligence was due to his knowledge of positive Wassermann and Kahn reactions of the blood was undetermined. During his sixteen days in the hospital he was

given twenty-three hours of Hypertherm treatment, in five sessions, and vision improved to 20/50 in the affected eye

CASE 37—This case was similar in all respects to cases 23 and 24. Vision was 20/50 on the patient's admission. Twenty hours of the Hypertherm treatment was given, in four sessions, and there was complete resorption, the final vision being 20/20.

SYPHILITIC KERATITIS

The immediate relief of the great pain and severe photophobia obtained with Hypertherm therapy in treatment of the early stages of syphilitic interstitial keratitis is remarkable. Since the beneficiaries of the United States Marine Hospital are rarely under the age of 20, there were only 4 cases of this condition in the present series, and whenever the Hypertherm treatment could be given the results were uniformly good. There follow the 4 brief case summaries.

CASE 29—A 22 year old man was admitted with congenital syphilis and interstitial keratitis of the right eye. Vision at the time of his admission was 4/200 in this eye. Only one Hypertherm treatment, of five hours, was given. Although there was immediate relief of the pain and the photophobia, further treatments were not deemed advisable, as the patient had convulsions while in the cabinet. In two months the vision had improved to 20/120, but the same condition had now appeared in the fellow eye. This was the only untoward reaction to the Hypertherm therapy which occurred in the series here presented. It is believed that further treatment would have been of great benefit.

CASE 31—A 32 year old man was admitted with severe interstitial keratitis of the left eye and congenital syphilis. He received forty-five and one-half hours of Hypertherm treatment, in five sessions. The pain and photophobia disappeared completely after the first treatment. In four weeks the cornea had cleared peripherally, there remained a central opacity. Complete clearance, with vision of 20/20, occurred four and one-half months later.

CASE 33—A man aged 20 was admitted with interstitial keratitis in the right eye and with vision limited to perception of light. He received fourteen hours of Hypertherm treatment, in five sessions. All pain and photophobia subsided with the first treatment. Vision on discharge was only 20/200, but he had had a divergent strabismus since childhood, and, since the media were clear and the fundus was normal, it is believed he had amblyopia ex anopsia in this eye.

CASE 35—A man aged 20 was admitted with interstitial keratitis of the left eye and congenital syphilis. Vision in this eye was 20/50 and had been recorded as 20/20 just four days before, during the course of a routine examination. He received thirty-six hours of Hypertherm treatment, in seven sessions, and there was immediate improvement, as well as relief from all pain and photophobia. A residual central corneal opacity was present three months later, but vision was 20/30, and there were no signs of activity.

COMMENT

It is apparent that the series of cases herein presented is too small to warrant any dogmatic conclusions. The results obtained with the use of the Kettering Hypertherm to induce artificial fever in addition

to specific syphilitic chemotherapy and the usual ophthalmic remedies, are definitely encouraging. The Hypertherm therapy is a means of treatment which is available in many of our hospitals but, to judge from the literature, is in relatively rare use in the treatment of ophthalmic disease.

Despite the fact that special nursing is required and that a careful physical evaluation must be made before each individual treatment, it is believed that the method is a most valuable addition to the all too limited armamentarium of ocular therapeutics. It is felt that at present its usefulness is not properly recognized in many centers, and it is with this in mind that this small series of cases is presented.

SUMMARY

There are presented 35 cases of syphilitic ocular conditions in which specific antisyphilitic chemotherapy, the usual local ophthalmic therapeutic measures and the Kettering Hypertherm were employed.

Of 19 cases of syphilitic atrophy of the optic nerve, improvement resulted in 4, or 21 per cent, clinical progression of symptoms was arrested in 7, or 37 per cent, and in 6, or 32 per cent, the disease either continued to progress despite, or had its onset during, Kettering Hypertherm treatment used in conjunction with other (standard) methods of therapy.

In the treatment of syphilitic choroiditis, this method of artificially induced fever therapy is valuable, particularly so when the lesions are fresh. It was employed in 6 cases of the acute form and resulted in decided improvement in 4, or 67 per cent. In the other 2 cases old, quiescent lesions were present.

The method is especially valuable when employed in the treatment of the form of acute iritis associated with secondary syphilis and affords a rapid form of treatment of this condition. Six cases of this type appeared in our series, in all of which excellent therapeutic results were obtained.

The method is definitely beneficial in the treatment of syphilitic interstitial keratitis, and it is most helpful in alleviating the severe pain and photophobia which are often associated with this condition.

PARTIAL CATARACT IN MEN OF MILITARY AGE

WING COMMANDER J H DOGGART, M.D., F.R.C.S.
ROYAL AIR FORCE

GENERAL SIGNIFICANCE OF CATARACT IN THE FORCES

ALTHOUGH the word "cataract" is often understood to mean a serious disturbance of the lens in one or both eyes, it has a less sinister significance in ophthalmologic circles, where cataract is defined as a partial or complete decrease in the transparency of the lens. Thus, the term used in its technical sense embraces numerous examples of lenticular opacities which are innocent in that they are either stationary or else so slowly advancing as to entail no appreciable handicap within the average span of life. Therefore the bare information that a man has partial cataract cannot contribute to a just decision concerning disposal and pension rights. Before settling the problem of disposal, it is necessary that one know whether the cataract is such as to interfere with the proper performance of service duties, and, in the absence of any immediate disability, the next question is whether the opacity is likely to increase to such an extent as to disable the man before his time in the service is completed. Then, again, in the assessment of claims for a pension or some other form of compensation, the assessor will ask to what extent, if any, a disabling form of cataract has been caused by service conditions. Sometimes the query is raised, concerning the victim of a partial cataract, whether his condition will be likely to deteriorate as a result of future service under special conditions, e.g., of climate.

It is not suggested that such questions can always be answered with complete certainty. In a large number of instances, however, it is possible to state emphatically that a given form of opacity is harmless and stationary, that another will soon proceed to complete opacification, that a third is due to trauma, and so on. There will also be many cases in which, though judgment has to be suspended at the original examination, a high degree of probability in prognosis can be attained after repeated scrutiny at intervals. In other words, the differential morphology of lenticular opacities is not merely of academic importance but supplies a practical clue to the past, as well as a signpost indicating the chances of good vision in the future.

ORIGIN AND SCOPE OF THIS INVESTIGATION

The survey presently to be described arose out of the interest shown by the Medical Directorate of the Royal Air Force concerning the relative frequency and practical significance of certain forms of opacities of the lens among men of military age. Coronary cataract was a subject to which particular attention was drawn, and some initial doubt was felt concerning its alleged incidence of 25 per cent in the adult population. At the same time it was realized that this figure could not be disregarded, emanating, as it did, from Vogt¹ (1930), who was the greatest authority in the world on slit lamp microscopy of the living eye. It seemed, however, that, even if Vogt's figure of 25 per cent were applicable to a cross section of the Royal Air Force, something might be gained by estimating the incidence of coronary and other forms of cataract so far as they could be detected without recourse to mydriatic drugs and the slit lamp.

In accordance with the last-mentioned suggestion, the figures and percentages given will apply, except when it is stated otherwise, to persons whose eyes were examined through the undilated pupil with the aid of focal illumination and with tenfold magnification by means of a loupe. From the practical aspect of a man's utility to the service, it may here be emphasized that in the great majority of instances a serious lenticular opacity can be detected through the normal pupil. This feature is well exemplified by complicated cataract, which arises as a result of intraocular disease, e. g., uveitis, retinitis pigmentosa or detachment of the retina. In a case of complicated cataract the first portion of the lens to undergo opacification is the hindmost layer of the posterior cortex, at the posterior pole, i. e., in the axis of the lens, where the lesion can be seen without mydriasis. In cases of this type, of course, the examiner should then proceed to enlarge the pupil, for the purpose of obtaining a more complete view of the lens, together with information about the intraocular disease of which the cataract is a complication, but a mydriatic would not be essential for its detection at the outset. In contrast to the foregoing type, coronary cataract may be cited as an example of benign lenticular opacity, which, in its early stages, would not be detected through the undilated pupil, and no harm would result from its being overlooked, because this condition calls for no treatment and hardly ever gives rise to symptoms.

Of the 300 persons included in the present survey, some lenticular opacity was visible by means of focal illumination and a loupe in all but 17, i. e., in 94.3 per cent and when, as a matter of interest, the apparently unaffected 17 persons were examined with the slit lamp, all but 6 proved

¹ Vogt, A. *Lehrbuch und Atlas der Spaltlampenmikroskopie des lebenden Auges*, Berlin, Julius Springer 1930, vol. 2, p. 455.

to have cataract in the technical sense of that expression. It is also noteworthy that 4 out of the 6 exceptions had pupils of less than average diameter. Therefore it may reasonably be assumed that when the lens is adequately exposed by mydriasis and inspected with the usual magnification of the slit lamp, viz., twenty-three times, some opacity will nearly always come to light. In the great majority of instances, however, no disability arises, for two main reasons:

- 1 The peripheral situation of the opacity. In this connection it must be remembered that even in darkness the pupil does not fully dilate, so that a large amount of cataractous change is compatible with good vision so long as the axis of the lens remains relatively unaffected.

- 2 The small size of the opacity. Normal acuity of vision was noted in many persons whose fetal nucleus was abundantly studded with opaque dots. In other words, even the axial portion of the lens may contain much opacity without detriment to sight if only there are no large continuous plaques of cataract.

METHOD OF APPROACH

Most of the 300 subjects included in this survey were candidates attending the no. 1 Central Medical Board, Royal Air Force, and were chosen at random. Their ages ranged from 19 to 60, with an average of 28.2 years. Of the number, 189 (63 per cent) were air crew members, and the other 111 (37 per cent) were engaged in various forms of ground duty. In each case immediate notes were made concerning any opacity rendered visible by the magnification (ten times) that a monocular loupe affords. It will be found that the calculated percentage incidences of the various types of opacity add up to considerably more than a 100, simply because one person may display several different forms of opacity. There are, in fact, some kinds of cataract, e.g., the dilacerated type, which never present themselves as an isolated condition.

ORIENTATION OF THE NORMAL LENS

That portion of the lens which is formed before birth is known as the fetal nucleus and is precisely limited by the two Y-shaped sutures, of which the anterior is an erect Y and the posterior an inverted one, thus λ . Figure 1 *A* demonstrates that these sutures are very near the capsule of the lens at the time of birth. Thereafter the lens continues to develop by the superimposition of successive layers of fibers derived from those of the anterior epithelial cells that abut on the equator of the lens. The result has been aptly compared to an onion, and figure 1 *B* shows a schematic optical section of the lens in later life. It is described as schematic advisedly, because in reality it would be impossible for all the different layers to be simultaneously in focus. The band of disjunction nearest the Y-shaped sutures in front and behind is known as the surface of the adult nucleus, which is formed at the age of about 14 years.

After puberty the nucleus of the lens, according to the usual terminology, includes both the adult and the fetal nucleus, and all the layers between the adult nucleus and the capsule of the lens are known collectively as the cortex. As time goes on, subsidiary bands of disjunction may become evident within these cortical layers. The small corkscrew tag attached to the posterior capsule of the lens in figure 1 *B* is a remnant of the

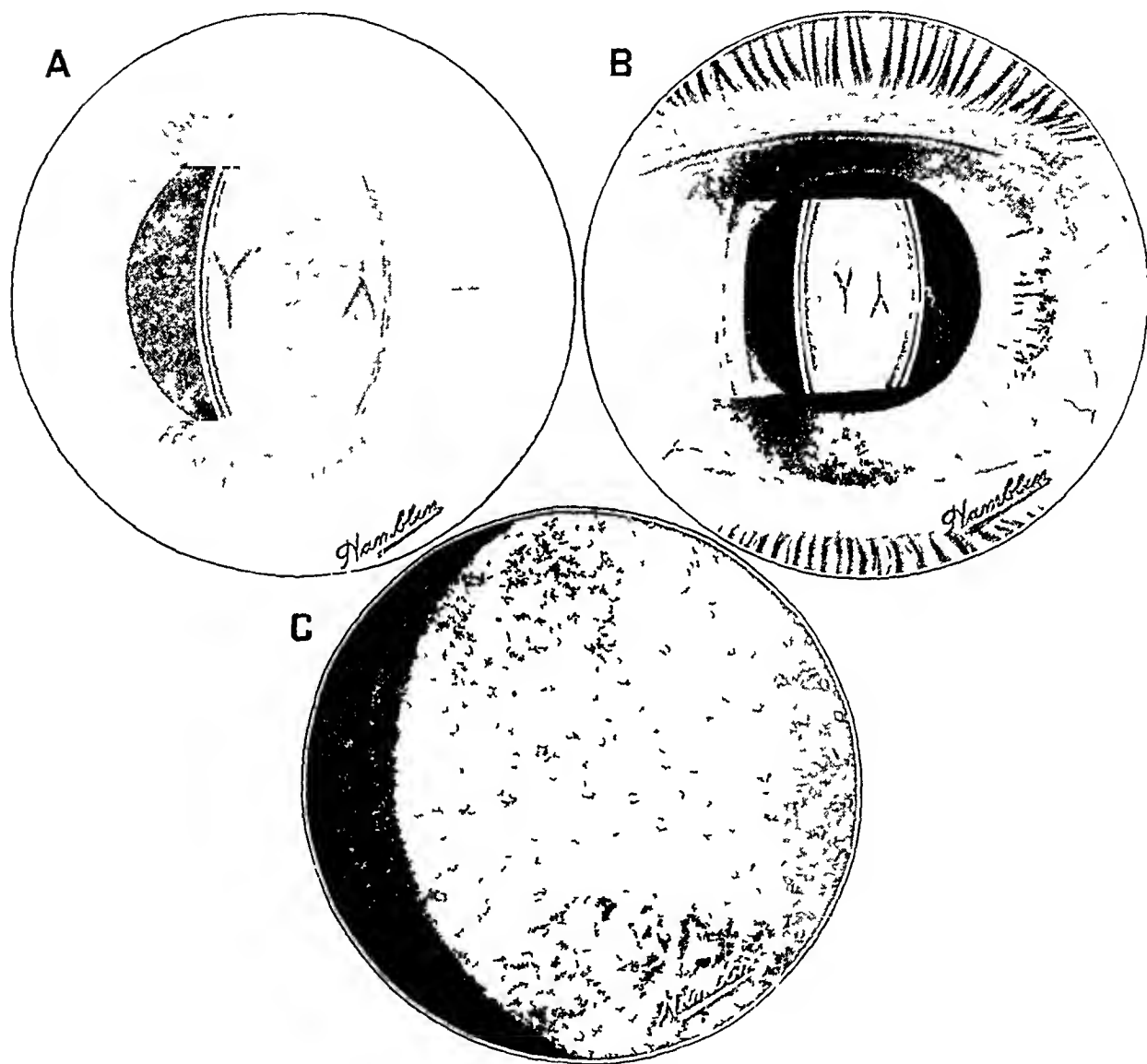


Fig 1—*A*, optical section of the lens soon after birth, *B*, optical section of the adult eye, *C*, epicapsular stars and scattered dots of cortical opacity

posterior hyaloid artery, which during intrauterine life extends from the optic disk forward through the vitreous, to break into branches on the back of the lens.

When once the orientation of the normal lens is grasped, it becomes easy to visualize the different kinds of cataract, without the necessity of elaborate description. If it is stated for instance, that a man's right

lens contains five blue dots of opacity situated in the axial region of the anterior cortex, and involving only those layers that lie immediately behind the anterior capsule, enough information has been supplied to make possible the construction of a mental diagram

RESULTS OF THE INVESTIGATION

Noncataractous Lesions of the Lens—There are several conditions which, although not strictly speaking of cataract, yet necessarily obtrude themselves on the attention of any one engaged in examining lenses. Of such the commonest are (1) deposits of pigment on the anterior capsule of the lens, (2) persistent pupillary membrane and (3) vacuoles or clefts containing fluid

1 *Epicapsular Pigment* Such pigment, in stellate form, was encountered in 58 cases (19.3 per cent). In figure 1 C will be seen two clumps of such brown stars, characterized by delicate jutting processes. Their practical importance lies in being often mistaken, especially when profuse, for the signs of old iridocyclitis. They represent, in fact, a congenital deposit, first described by Schleich² (1882). It was estimated by Rumbaur³ (1921) that they can be found in about 35 per cent of all persons, but the figure of 19.3 per cent obtained in the present survey, is not unduly low in view of the fact that a mydriatic was not used. Peripheral clumps of stars are, of course, covered by the iris until the pupil is dilated.

Amorphous granules of pigment adhering to the anterior capsule of the lens are derived from the pigment layer of the iris, as a result of trauma or inflammation. No traumatic deposits were seen in the present series, which, however, contained 2 cases (0.7 per cent) of brown epicapsular granules due to previous iridocyclitis.

(2) *Persistent Pupillary Membrane* One or more strands of such a membrane were detected in 42 cases (13 per cent)—a figure considerably lower than that given by most authors. It should be remembered, however, that higher estimates of the incidence of persistent pupillary membrane will always be obtained by the use of the slit lamp, because this instrument enables an observer to see short, slender filaments, which escape detection with a loupe.

In figure 3 the presence of an anterior capsular cataract, to which adhere two strands of persistent pupillary membrane, is a special feature of the case illustrated. In most cases, however, it will be found that each strand is disposed in one of two positions (*a*) floating freely from a single attachment, as in the case of the strand on the right side of figure 8,

2 Schleich Mitth. a. d. ophth. Klin. in Tübing. 1, 1, 1882

3 Rumbaur Klin. Monatsbl. f. Augenh. 66, 737, 1921

01 (b) crossing from one point to another of the lesser circle of the iris. This lesser circle, from which all strands of persistent pupillary membrane take origin, is also known as the collaret. It is situated on the anterior surface of the iris, usually about two-thirds the distance from the ciliary to the pupillary margin.

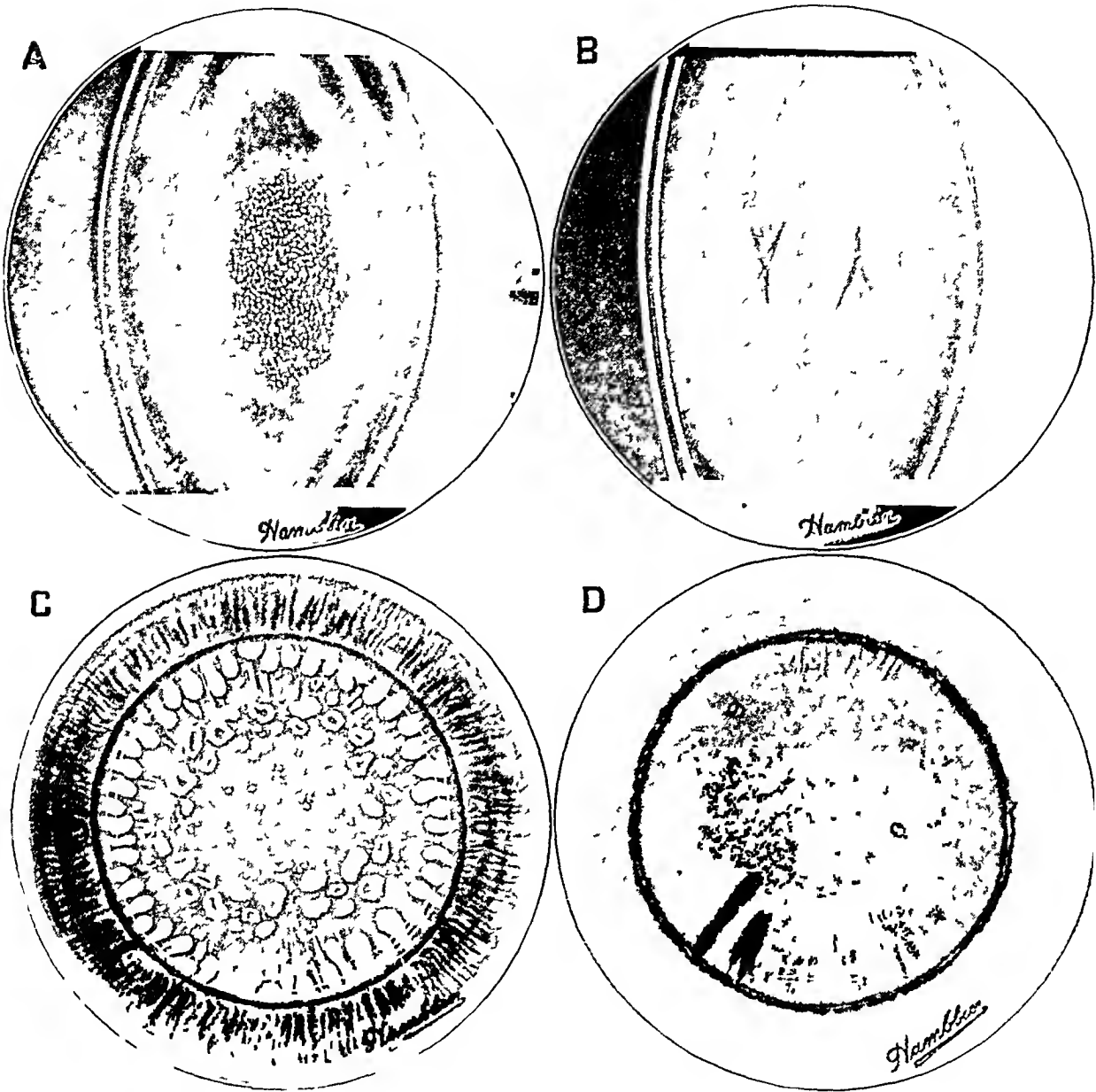


Fig 2—A, cataract consisting of close-set dots in the fetal nucleus, B, anterior axial embryonic cataract, C, coronary cataract, D, semile cuneiform cataract, fluid vacuoles and clefts

Strands of persistent pupillary membrane are, of course, remnants of the anterior vascular sheath by which the lens is covered during intra-uterine life. They are seldom dense enough to obstruct vision, so that their chief clinical importance is a liability to be misinterpreted as

posterior synechias from old iridocyclitis. In the great majority of irises the collaret, from which all strands arise, is separated by an appreciable interval from the pupillary margin, to which latter structure posterior synechias are anchored.

3 Fluid Vacuoles. Such vacuoles are not uncommonly seen, especially in the cortical layers, among adults of all ages. Ten cases (6.3 per cent) were noted in the present series. The proportion would, of course, be much higher in a series of older people examined with dilated pupils. Figure 2D displays two vacuoles in the lens of a man aged 60, who was also found to be suffering from early senile cataract.

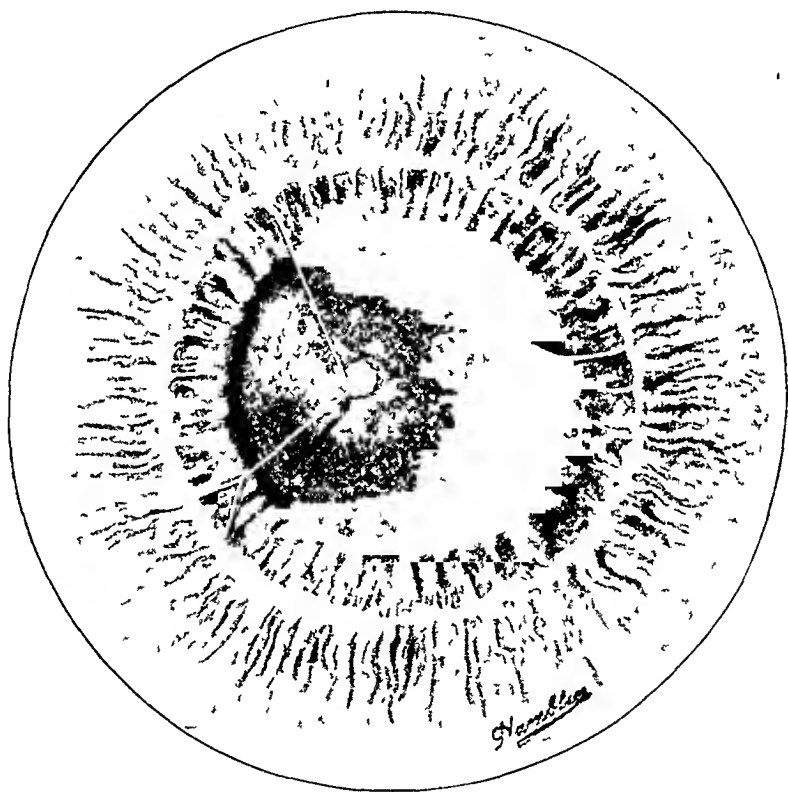


Fig 3—Anterior capsular cataract with persistent pupillary membrane adherent to it.

This form of opacity will be mentioned later in the paper. At present it will suffice to draw attention to another form of fluid collection, viz, fluid clefts, as represented in the lower left corner of figure 2D. Such clefts are in many instances jagged and irregular in shape. Together with fluid vacuoles, they can, even in the absence of true opacity, interfere seriously with vision, by rendering refraction irregular, when they occupy the axial portion of the lens in large numbers.

Types of Cataract—The types of cataract found among the 300 subjects studied are given here, in order of their frequency.

1 Scattered Dots Involving Cortex or Adult Nucleus or Both In some cases only two or three dots were revealed In others the dots were so abundant as to constitute the condition known as "dusty cataract in concentric layers" In 279 cases (93 per cent) one or more dots of opacity could be seen in one or both lenses, without mydriasis, and under the magnification of only a loupe Figure 1 *C* shows the appearance of a multitude of dots Besides the scattered dots which represent the only form of opacity, there are many kinds of cataract, e g, those depicted in figures 2 *C* and 4, which may exhibit opaque dots in addition to their own characteristic designs

2 Multiple Dots in Fetal Nucleus These central dots are often known collectively as *cataracta centralis pulverulenta* A typical case is shown in figure 2 *A*, in which it will be noted that the other layers of the lens are uniformly transparent The presence of dots in the fetal nucleus does not, however, preclude involvement of other layers, so that not uncommonly this variety of cataract will be found in association with the preceding kind These central dots are usually too small to impair the visual acuity, but they may render the optic disk somewhat blurred More than once I have seen a case in which early papilledema was suspected, when, in fact, the ophthalmoscopic appearances were amply explained by this concentration of opaque dots in the axial region of the lens The present series contained 65 instances (21.7 per cent) of cataract implicating the fetal nucleus, i e, the innermost core of the lens, bounded in front and behind by the Y-shaped sutures

3 Coronary Cataract This type was found in 18 cases (6 per cent), but this observation does not conflict with the figure of 25 per cent, estimated by Vogt (1930) and other authorities, for the following reasons

(a) In its earlier and less developed stages coronary cataract is not, as a rule, accessible to view without mydriasis

(b) The average age of persons in the present series, viz, 28.2 years, is lower than the average age of the adult outpatient population of a civilian hospital, from which type of practice the statistics of Vogt and others were gleaned In this connection, it is perhaps of interest to note that the average age of the 18 patients displaying coronary cataract in the present series was 35.2 years, i e, considerably higher than that of the series as a whole One may therefore legitimately conclude that these 18 patients had relatively advanced coronary cataract and that many of the persons in whom examination revealed scattered dots of opacity would have proved to have coronary cataract if the pupils had been dilated

As a supplement to the investigation of 300 subjects through the undilated pupil by means of a loupe, the opportunity subsequently arose to inspect with the slit lamp a random series of 100 men in whom mydriasis was desired for some other reason, e g, examination of the fundus. Among 100 subjects, with an average age of 27.7 years, there were 23 cases of coronary cataract—a figure which represents the true normal incidence in a way that is impossible for a series examined without a mydriatic.

Figure 2 C demonstrates, in a typical case of advanced coronary cataract that the essential kind of opacity in this condition is club shaped, with its broader end directed toward the axis, and that the clubs are disposed around the periphery of the lens. In addition to these characteristic clubs, there are nearly always to be found a number of

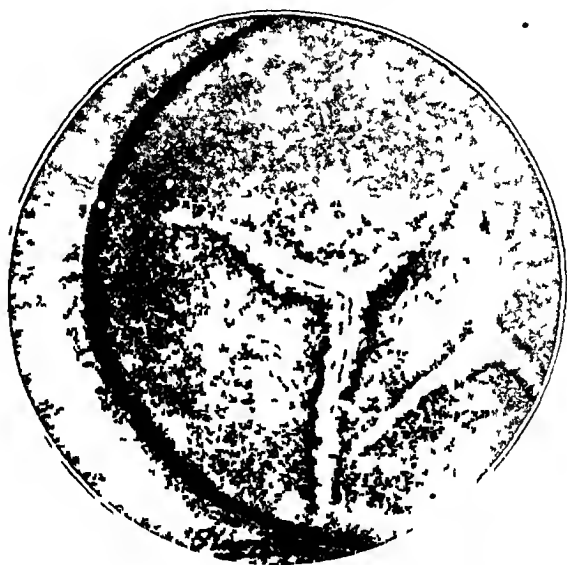


Fig 4—Suture cataract, dilacerated cataract

scattered dots, together with nummular dots and dots of other shapes. A blue or green tinge may be evident in some opacities, and the occurrence of scattered crystals is by no means rare.

4. *Anterior Axial Embryonic Cataract* In this type the opacities are clustered immediately in front and behind the anterior Y-shaped suture, as indicated in figure 2 B. This form was found in 12 cases (4 per cent).

5. *Dilacerated Cataract* The incidence of this type was 4 cases (1.3 per cent). Figure 4 exemplifies the aforementioned observation that this type of opacity always occurs in association with one or more other forms of cataract. The suture cataract in this diagram will be discussed presently, the scattered dots require no further comment, but the pan-

of dilacerated cataracts may readily be recognized by their complex, teased-out structure, not unlike pieces of coral. They possess a blue tinge, which is fortuitous.

6 Suture Cataract. The Y-shaped sutures are thrown into prominence by an abundant series of opaque dots. As a rule, the anterior Y is more decisively mapped out than is the posterior one. Figure 4 shows a typical instance, but sometimes a more complicated design comes to light in which a series of petal-shaped opacities are disposed in the track of the Y-sutures. Such opacities are often called floriform cataract. The present series contained 3 instances of suture cataract (1 per cent).

7 Anterior Capsular Cataract. This type also occurred in 3 cases (1 per cent). The cataract which is represented in figure 3 gave attachment to strands of persistent pupillary membrane, but this feature was lacking in the other 2 cases.

8 Senile Cataract. Finally, there was a single instance (0.3 per cent) of senile cataract, but it must be emphasized that an early stage of this condition would certainly have been revealed in a larger percentage of cases if the pupils had been dilated. Figure 2 D demonstrates the typical wedge shape of the opacities. Admittedly, there are other forms of senile cataract, but the cuneiform variety is the commonest. It usually arises in the superficial and middle layers of the cortex, in contrast to coronary clubs, which implicate the deeper layers of the cortex and the superficial layers of the adult nucleus. But the morphologic contrast between coronary and senile cataract (fig. 2 C and D) is sufficiently striking to distinguish the two, without the necessity of estimating exactly which layers are involved, and the only case in which a novice might be confused is one in which the two conditions occur together. The possessor of coronary cataracts is not immune to the onset of senile opacity, so that as time goes on his lenses may be found to contain wedges as well as clubs.

Comment—The most important fact emerging from this survey is that, although the incidence of cataract proved to be 94.3 per cent, even under the restricted conditions of examination (i.e., without mydriasis and the slit lamp), the series contained not a single instance of defective visual acuity for which the cataract could be fairly blamed. In the small minority of cases in which vision was not correctable to 6/6 in each eye there was always an obvious reason for the defect. Here is a typical instance. An accountant officer, aged 33, showed bilateral dusty cataract in concentric layers, and his vision was correctable to 6/6 in the right eye and to 6/24 in the left eye. Inquiry revealed, however, that left internal squint had been present during several years of his childhood. Moreover, the refractive error in his left eye viz., compound hyper-

metropic astigmatism, was higher than that in his right eye. Furthermore, he showed no discrepancy between the two lenses in respect to the size and density of their opaque dots. Such concatenation of evidence justifies a diagnosis of amblyopia of the left eye, i. e., a visual defect incommensurate with the state of the fundus or the media.

With the exception of senile cataract, the presence of which in an advanced form is not common among healthy men of military age, all the aforementioned forms of cataract are harmless and stationary or else so slowly progressive as hardly ever to exert any decisive influence on a man's fitness for duty.

One final comment is needed before the results are summarized. There were no instances of "medical" cataract, i. e., cataract attributable to a hormonal or metabolic disorder. "Medical" cataract may arise in certain cases of such conditions as juvenile diabetes, cretinism, parathyroid disease, mongolism and myotonia atrophica. No surprise need be felt at the absence of such cases in this series, because (a) many of the causative conditions are such as would automatically render their victim ineligible for admission to the service, (b) some of the diseases are rare, and (c) even in the case of a less rare condition, such as diabetes, it must be remembered that only a small minority of diabetic patients are afflicted with the diabetic cataract.

SUMMARY OF INVESTIGATION

1 Three hundred men, selected at random, and not complaining of ocular symptoms, were searched for the presence of cataract, so far as that condition is accessible to view through the undilated pupil under the magnification of a loupe.

2 Their ages ranged from 19 to 60 years, with an average of 28.2 years. The percentages of all crew members and ground staff were, respectively, 63 and 37.

3 The total incidence of cataract was 94.3 per cent. Many of the men displayed more than one form of opacity, so that the percentages of the individual types of cataract totaled more than 100. The distribution was as follows:

Type of Cataract	Percentage
Scattered dots (including dustlike cataract in concentric layers)	93.0
Cataracta centralis pulverulenta	21.7
Coronary cataract	6.0
Anterior axial embryonic cataract	4.0
Dilacerated cataract	1.3

Suture cataract	10
Anterior capsular cataract	10
Senile cataract	03

4 Certain closely related, though noncataractous, conditions were found with the following frequency

	Percentage
Epicapsular pigment	
Stellate	19.3
Amorphous	0.7
Persistent pupillary membrane	13
Fluid vacuoles	6.3

5 The incidence of corionary cataract (6 per cent) under the restricted conditions of examination was found to be considerably exceeded by that (23 per cent) in a series of men subjected to mydriasis and with the microscopic examination slit lamp

6 There were no cases of defective visual acuity attributable to the types of cataract found or any cases of cataract indicative of special systemic diseases

PRACTICAL APPLICATIONS

1 Cataract is so common, and so harmless in the vast majority of instances, that its slighter forms need not be described when they come to light in the routine clinical examination of persons free from ocular symptoms

2 The mere statement that a man has partial cataract supplies no useful guidance. If an ophthalmologist commits himself to remarking on the presence of a partial cataract, he should indicate his opinion as to whether or not the condition is trivial. If he considers that it is not trivial, he should say whether the cataract is regarded as immediately serious or as serious on account of its probable future extension. If he feels unable to offer a prognosis until he has had the opportunity to examine the patient repeatedly at intervals, he should not hesitate to demand such additional examinations.

3 Prognosis based on the differential morphology of opacities of the lens does not claim to be infallible, because absolute certainty can rarely be attained in any aspect of medicine or surgery. Such attempts at prognosis can, however, indicate the probable outcome in a large number of cases encountered, and the proportion of correct guesses will be at its highest when phenomena patiently observed are interpreted in the light of established research.

THE CORNEA

VIII Permeability of the Excised Cornea to Ions, as Determined by Measurements of Impedance

MARGARET HOLT, Ph D

AND

DAVID G COGAN, M D

BOSTON

IN CONNECTION with recent studies of the permeability and other properties of the excised cornea,¹ measurements of electrical impedance might be expected to give additional pertinent information. It is now generally accepted that the impedance of biologic tissues is directly related to their ionic permeability.² In the same way that measurements of impedance of solutions of pure electrolytes may be considered to measure (aside from concentration effects) the ability of the ions to diffuse through the medium, measurements of impedance of the cornea may be considered to give a measure of the ability of the ions to move through the tissue.

The impedance consists of a resistive component, related to movement of ions in an electrolyte (and thus generally accepted to be a measure of permeability to ions), and a capacitative component, probably associated with dielectric properties and polarization of the tissue. The resistive component is of principal interest in the measurements to be reported, and the capacitative component is automatically balanced out by the experimental procedure.

Measurements of impedance are rapidly and easily carried out with the aid of an ordinary alternating current bridge. They are quantitative and reproducible and require only a fraction of the time involved in making most chemical analyses. In the study of permeability, measurements of impedance supplement the usual chemical methods in providing a means for studying instantaneous permeability to ions. Measurements of impedance taken at intervals over a long period provide the best method for determining how the permeability of the cornea changes with time and what the "normal" permeability of the excised cornea is to ions under a given set of conditions. Measurements of

From the Howe Laboratory of Ophthalmology, Harvard Medical School

1 Cogan, D G, Hirsch, E O, and Kinsey, V E. The Cornea. VI Permeability Characteristics of the Excised Cornea, *Arch Ophth* **31** 408-412 (May) 1944

2 Davson, H, and Danielli, J F. The Permeability of Natural Membranes, London, Cambridge University Press, 1943, p 204

impedance also make it possible to determine the reversibility of an observed effect, and with one cornea it is possible to change the conditions of the experiment several times during a single period of observation. Measurements of impedance, however, do not have the specificity of chemical analyses, so that differential permeability to the various ions in a mixture cannot be readily determined, moreover, the measurements give no index of the permeability to nonionized substances.

PROCEDURE

The impedance of excised corneas was determined under various conditions. Whole beef eyes were obtained within a few hours³ after the animals were slaughtered. The corneas were prepared by excision at the limbus, removal of the

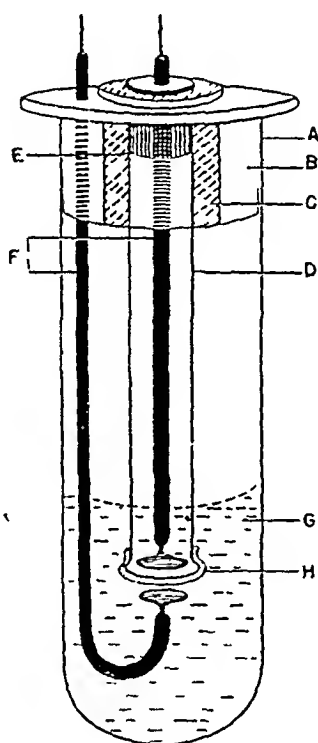


Fig 1—Conductivity cell. *A* indicates outer tube, which is immersed in a temperature bath, *B*, Bakelite stopper into which the lower electrode is sealed in a permanent position, *C*, inner Bakelite stopper into which tube *D* fits snugly, *D*, glass tube, which may be slipped in and out of the stopper (the cornea is tied on the flared end of the tube), *E*, small Bakelite stopper which fits into *C* and holds the upper electrode, *F*, glass tube with platinized platinum electrode sealed in the end and filled with mercury (indicated by shading), *G*, solution in cell, and *H*, cornea.

endothelium and, in some cases, removal of the epithelium according to a technic previously described⁴. The cornea was then securely tied onto the flared end of

³ The results were essentially the same with beef corneas used within the first hour after death of the animal as with the corneas left on the enucleated eye at room temperature for as long as six hours before the experiment was started.

⁴ Cogan, D. G., and Kinsey, V. E. The Cornea. I. Transfer of Water and Sodium Chloride by Osmosis and Diffusion Through the Excised Cornea, *Arch. Ophth.* 27: 466-476 (March) 1942.

the tube in the conductivity cell and so placed that the outer surface of the cornea faced the inner portion of the tube

The conductivity cell (fig 1) consisted of (1) an inner glass tube, holding the cornea on its lower orifice and containing one of the electrodes immersed in the particular solution that was being used, and (2) an outer glass tube, containing the other electrode and the same solution as that in the inner tube. The electrodes consisted of platinum (platinized) circular foot plates (0.8 sq cm) connected with the bridge circuit by a column of mercury. During the measurement the electrodes were "separated from each other" by the cornea and some of the solution. Both the inner and the outer tube were covered with Bakelite and Lucite stoppers. The inner tube, with the inner electrode, could be readily removed and reset at its original position.

The area of the cornea exposed to the solution in the inner tube was approximately 1.1 sq cm.

Six conductivity cells were immersed in a bath the temperature of which was maintained by a mercury thermoregulator at $25 (\pm 0.02)^\circ\text{C}$. The conductivity

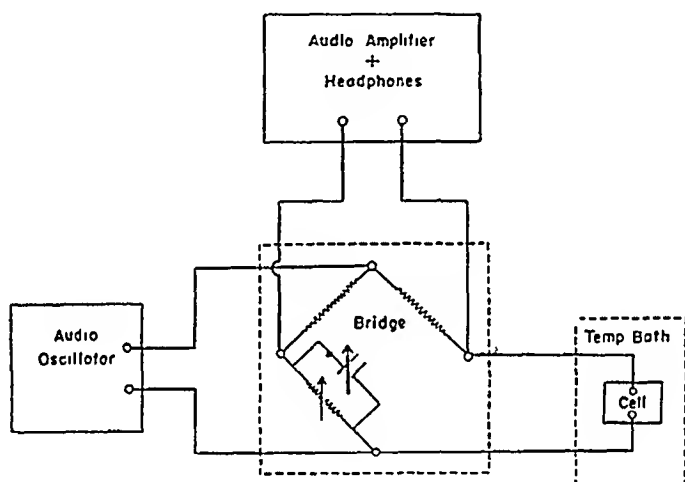


Fig 2—Block diagram of equipment

tubes were all of approximately the same dimensions (inside diameter of tube, 12 mm). All the results reported represented the average results obtained from all 6 tubes.

The resistance and capacitance of the separate corneas were determined by comparing the resistance of each cell containing the cornea with known resistances, as indicated in figure 2, and corrected for the blank obtained when no cornea was present. The audio oscillator circuit used was the Hewlett Packard series 200 type, the bridge circuit was a modified Wheatstone type, and the audio amplifier was of standard design. All measurements reported here were made at the frequency of 1,000 cycles per second. The input to the bridge was kept down to approximately 10 millivolts, i. e., less than would be expected to stimulate or damage a tissue.⁵

⁵ See, for example, Coppee, G. Stimulation by Alternating Current, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, pp. 150-162.

The blanks were obtained by measuring the resistance and capacitance of the solutions in the conductivity cell before affixing the corneas to the tubes and, at the end of the experiment, after the corneas had been removed. The variation in the two measurements was ± 0.5 ohm, corresponding to an accuracy of ± 0.1 per cent in the resistances of the cornea (epithelium and stroma combined). This variation was less than that introduced by factors other than electrical measurements.

The resistances obtained with blanks were subtracted from those obtained when the corneas were in place, and the resultant measurements were taken to represent the true value for the cornea.

At the end of each experiment the integrity of the epithelium was checked in the usual way by means of sodium fluoresceinate¹.

RESULTS

The measurements of the initial resistance and capacitance of the epithelium-stroma combination and of the stroma only, corrected for the blanks and determined within five to ten minutes after excision of the cornea from the enucleated beef eye, are recorded in the table. Both sides of the cornea were immersed in 0.9 per cent solution of sodium chloride.

*Measurements of Initial Resistance and Capacitance of the Epithelium-Stroma Combination and the Stroma Only**

Epithelium and Stroma		Stroma	
Resistance, Ω	Capacitance, μf	Resistance, Ω	Capacitance, μf
441	0.18	5	0.01
439	0.21	3	0.01
515	0.17	5	0.01
467	0.19	7	0.01
411	0.18	5	0.01
400	0.16	8	0.01
308	0.19	5	0.01
428	0.07	6	0.01

* The tissues were immersed in 0.9 per cent sodium chloride, at a temperature of 25°C.

The average resistance of 0.9 per cent solution of sodium chloride in the cells, measured before the corneas were added, was 40 ohms. Addition of the stroma resulted in an average increase of resistance of 6 ohms, whereas addition of the epithelium-stroma combination resulted in an average increase in resistance of more than 400 ohms. Approximately the same results were obtained when Ringer's solution was substituted for 0.9 per cent solution of sodium chloride.

It thus appears that the stroma offers little resistance to the passage of ions, whereas the epithelium offers a relatively enormous resistance. These observations are in keeping with the results previously obtained by chemical procedures but go further in indicating that the impermeability of the epithelium previously determined chemically for isolated

ions is, in fact, applicable to all ions. Technical difficulties have prevented, so far, similar measurements being carried out for the endothelium.

The changes in resistance of 6 excised corneas with time are represented in figure 3, in which the resistance of the epithelium-stroma combination is compared with that of the stroma only. Again, the measurements were made with both surfaces of the cornea immersed in 0.9 per cent solution of sodium chloride, but similar results were obtained using Ringer's solution. The initial high resistance of the epithelium-stroma combination fell somewhat during the first two to three hours, at which time it reached a plateau that was maintained, at room temperature, for at least twenty-six hours. The capacitance varied inversely as the resistance for the first several hours.

Variation in resistance of the epithelium-stroma combination was determined under a variety of conditions induced by changing the

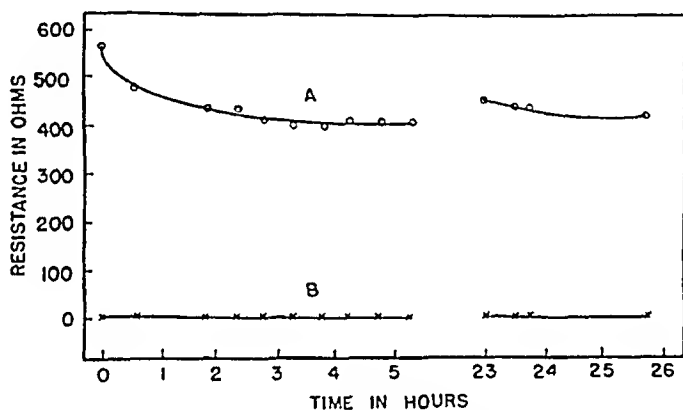


Fig. 3—Curve *A* shows the resistance of the epithelium-stroma combination bathed in 0.9 per cent solution of sodium chloride over relatively long periods. Curve *B* shows the resistance of the stroma after removal of the epithelium. The end curve represents the average of measurements on 6 corneas.

solutions bathing the cornea. A 25 per cent solution of sodium chloride resulted in a fall in resistance, so that at the end of eighty minutes the resistance of the cornea was only 17 per cent of its original value. When the 25 per cent solution of sodium chloride was replaced by 0.9 per cent sodium chloride and the resistance again measured, the effect was shown to be irreversible. Solutions containing 0.9 per cent of the following salts had essentially the same effect as 0.9 per cent solution of sodium chloride: calcium chloride, sodium nitrate, and mixtures of calcium chloride and sodium chloride, and of potassium chloride and sodium chloride. But, curiously, solutions of 0.9 per cent potassium chloride or of 0.9 per cent potassium sulfate in the absence of sodium chloride had a different effect. With these solutions the corneal resistance increased steadily until at the end of one hour

it was 115 per cent greater than its original value in the case of potassium chloride and 170 per cent greater in the case of potassium sulfate. The effect was slowly reversible, replacing the potassium salts with sodium chloride resulted in a return toward the original resistance, but at the end of forty minutes the corneal resistance was still about 50 per cent greater than normal.

A similar increase in resistance occurred with corneas immersed in phosphate buffers containing the potassium ion, and the amount of increase varied with the amount of the potassium ion. It is not the difference in hydrogen ion concentration which is responsible for the

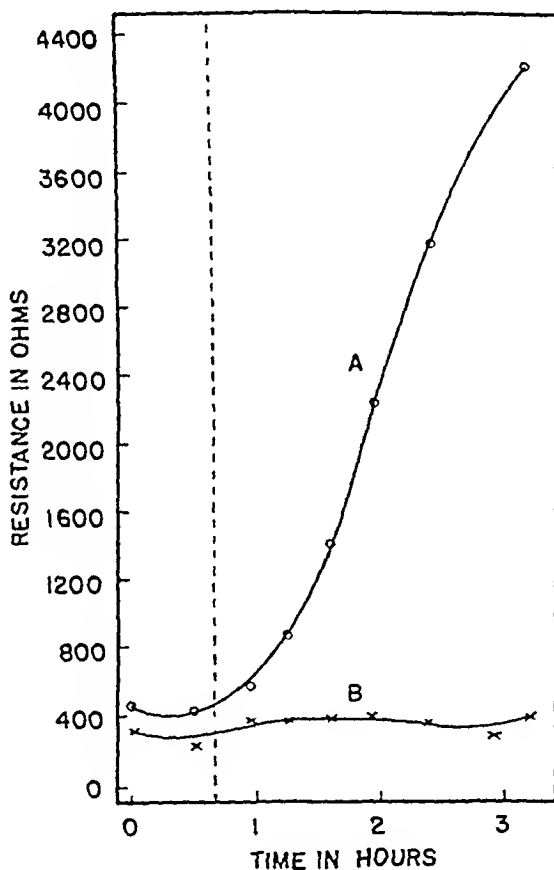


Fig 4—Curve *A*, effect on the resistance of the epithelium-stroma combination produced by potassium biphosphate (fifth-molar), which had been neutralized to p_H 6.5 by the addition of potassium hydroxide. Curve *B*, effect produced by sodium diphosphate (fifth-molar), which had been neutralized to p_H 6.5 by the addition of hydrochloric acid. Each curve represents the average of measurements on 3 corneas. The measurements indicated to the left of the vertical dotted line were made with the corneas in 0.9 per cent solution of sodium chloride, the dotted line indicates the time at which the solutions were changed.

changes in resistances when potassium is used, for, as seen in figure 4, solutions of sodium diphosphate neutralized by the addition of hydrochloric acid showed widely different effects on corneal resistance from those produced by potassium diphosphate neutralized by the addition of potassium hydroxide. At the same time, solutions of varying hydro-

gen ion concentrations showed the increased resistance so long as the potassium ion was present

We have no explanation for this curious effect of the potassium ion on corneal impedance and are not aware of any analogous effect of potassium on other biologic membranes

The effects of two alkaloid salts on corneal impedance were also studied. Atropine sulfate (10 per cent solution in 0.9 per cent sodium chloride) and cocaine hydrochloride (4 per cent solution in 0.9 per cent sodium chloride) resulted in a prompt increase in resistance, to a value approximately 50 per cent greater than the original value in the case of atropine and to a value 65 per cent greater in the case of cocaine within a period of ten minutes. This increased resistance was maintained for at least eighteen to twenty hours. The effects were rapidly reversible (also within ten minutes) at any time during this period when the alkaloid solutions were replaced by solution of sodium chloride, and the determination could be repeated several times.

All the foregoing effects with different solutions were due to alterations in the epithelial impedance. No changes in impedance occurred with the same solutions when the impedance of the stroma only was measured.

SUMMARY AND CONCLUSIONS

1. Electrical impedance of the excised cornea is considerable so long as the epithelium is present. The impedance of the stroma alone is slight. So far as impedance is an index of ionic permeability, this means that the epithelium offers considerable resistance to the passage of ions, whereas the stroma offers a resistance little more than that offered by an equivalent volume of isotonic solution of sodium chloride.

2. The initial impedance of the cornea falls within the first few hours after excision to a level approximately two-thirds its original value and is then maintained at this level for at least twenty-six hours at room temperature. Again, so far as this reflects permeability of the epithelium to ions, measurements of the excised cornea indicate a somewhat more leaky epithelium (in regard to ions) a few hours after excision than is the case for the fresh cornea. The corneal epithelium is, therefore, an even more effective semipermeable membrane than previous chemical measurements have shown it to be.

3. The impedance of the epithelium of the excised cornea is irreversibly decreased by bathing the cornea in 25 per cent sodium chloride, it is unaffected by 0.9 per cent solutions of sodium chloride, calcium chloride and sodium nitrate, and it is reversibly increased by 10 per cent atropine sulfate, by 4 per cent cocaine hydrochloride and, especially, by solutions in which the cation is the potassium ion.

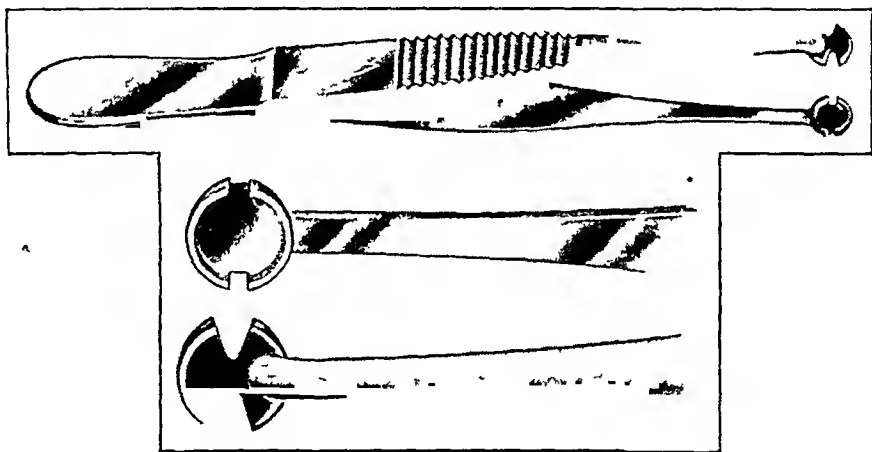
AN INSTRUMENT FOR KERATOPLASTY

New Forceps to Facilitate the Preparatory Suture of the Transplant

H ARRUGA, M D

BARCELONA, SPAIN

THE difficulty experienced in the passing of the suture thread through the transplant, even when very fine needles are used, in the endeavor to avoid bruising or contusing it, is due to the effort to reduce the pressure exerted on the forceps to a minimum, which pressure must be greater than that produced by the forcing of the needle through the corneal transplant



Forceps to facilitate preparatory suture of the corneal transplant

Special forceps have been made by Friede with the object of avoiding this trouble, but, although they cause less injury, they still squeeze the transplant

To reduce the lesion of the transplant to a minimum, I have designed forceps which allow the transplant to be securely held without any injury whatever resulting from overpressure during the process of making the preliminary sutures because no pressure applied to the forceps is imparted to the imprisoned transplant (figure)

At the extremities of the arms of the forceps is fitted a little pillbox-shaped container, just large enough to hold the transplant. The box portion, fitted to one arm of the forceps, is 4.2 mm in diameter by 0.7 mm deep while the cover portion, fitted to the other arm, simply covers the box and to a little depth, the side, in the same manner as the cover of a pillbox.

Two vertical slots are cut, one at each end of a diameter, through the cover and the box, the dimensions of these slots being just sufficient to allow the passage of the needles through the transplants to its border.

The transplant, 4 mm in diameter, with the epithelium side uppermost, is placed in the box portion of the forceps, the underside lying flat on the bottom of the box. The forceps are then closed, which brings the cover into position over and closes the box, leaving just enough of the cornea exposed at the two ends of the diameter through the slots already mentioned to allow the needles to be passed with the threads.

The needles are passed from the upper side near the border, at an angle, to come out halfway through the thickness of the disk of the corneal transplant.

It is important that the needles be well pointed and the suture material very fine.

Grieshaber, of Schaffhausen, Switzerland, supplies me with the needles, and Dugast, of Paris, with the suture thread.

The trephining is practiced with an ordinary trephine, 4 mm in diameter, and I use the instruments made by Grieshaber, of Schaffhausen.

Greater security is obtained in the fixing of the transplant with the method I describe than with the other methods which can be employed. This greater security is always a favorable factor in insuring satisfactory resulting optical functions of the corneal graft.

The suture threads leave minute spots in the corneal graft where these threads have passed, but in the great majority of cases these spots are invisible to the naked eye and do not impair the transparency of the corneal graft.

Pas Mendez Vigo (3)

Clinical Notes

SEESAW NYSTAGMUS ASSOCIATED WITH CHOROIDITIS AND POSITIVE NEUTRALIZATION TEST FOR TOXOPLASMA

C WILBUR RUCKER, M D, ROCHESTER, MINN

NYSTAGMUS in which one eye turns rhythmically up and down while its fellow moves contrarily, in the nature of a seesaw, is strange and rare. The only case that I have been able to find in the literature is one reported in 1914 by Maddox¹. In this report no mention was made of the site of the lesion or of its possible cause. In the case to be reported here there is likewise no evidence as to the site of the lesion, nor is the causative agent proved although a possible etiologic factor suggests itself.

REPORT OF A CASE

A white man, aged 51 came to the Mayo Clinic on Oct 11, 1944, complaining of loss of vision. His occupation had been that of attendant at a service station for automobiles. He had been myopic since childhood and had worn glasses for thirty years.

His present difficulty began four years prior to admission, when he noted failure in his vision and inability to read newspaper print. A physician whom he consulted found a defect in the visual fields. Two years later further deterioration had occurred in the visual acuity, and about that time he had blisters on his lips for several months. A year prior to his admission continuing loss of vision obliged him to give up driving his car. About that time his eyes began to jump. For six months before admission he had had humming tinnitus.

On examination at the clinic the visual acuity was recorded as 2/60 in the right eye and 3/60 in the left eye. There was a constant seesaw nystagmus. As the right eye turned up, the left turned down, and as the right turned down, the left turned up. The rate was 128 beats per minute, and the movement covered a distance of approximately 1 mm, the distance diminished slightly on gaze to the sides. Neither the rate nor the type of motion changed on shifting the direction of gaze. The movements of the right eye were almost entirely vertical. The movements of the left eye were mostly vertical, although there was also a rotary element, the eye rolling in with the upward phase and out with the downward phase. The pupils did not react to light but reacted fairly well in convergence.

Ophthalmoscopic examination disclosed the following picture. There was myopia of 4 D. The optic disks were tilted, their nasal portions were full and their temporal portions flat, depressed and bordered by broad choroidal crescents. There was moderate pallor of both disks. The entire choroid of both eyes appeared to be sclerotic and finely mottled with pigment. Nasally and superiorly the retinal pigment had migrated forward and accumulated around small veins.

From the Section on Ophthalmology, the Mayo Clinic

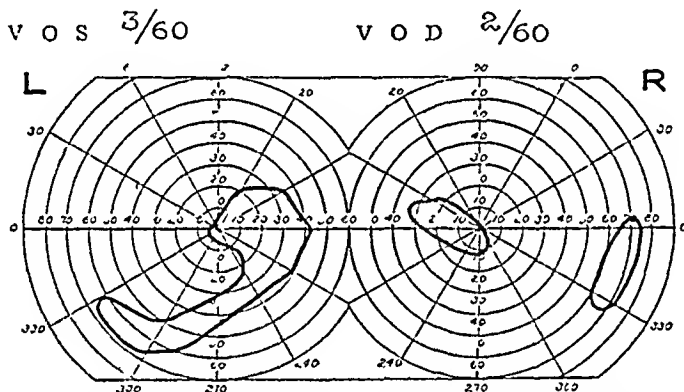
1 Maddox, E. E. See-Saw Nystagmus with Bitemporal Hemianopia, *Proc Roy Soc Med (Sect Neurol, Ophth & Otolaryng)* 8 (pt 2). xii-xiii (Feb 26) 1914

The retinal arterioles were greatly attenuated. The process appeared to be that of diffuse choroiditis of low grade.

The fields of vision were restricted to small isles, which were chiefly in the central and inferior temporal areas (figure).

Extensive examinations were conducted in an attempt to determine the cause of the patient's disorder. The following laboratory tests showed no deviation from normal: blood counts, urinalysis for albumin, sugar and lead, agglutination test of the blood for *Brucella abortus*, flocculation tests for syphilis, roentgenographic studies of the head and chest, and examination of the spinal fluid. General physical examination revealed no evidence of disease, and detailed neurologic examination disclosed no abnormalities except those noted previously by the ophthalmologist. A specimen of the patient's blood was sent to the Minnesota Department of Health and was reported to produce a slight to moderate neutralization against the organism *Toxoplasma*.

This laboratory report does not prove that *Toxoplasma* is the cause of the patient's difficulty. Heidelman,² in his evaluation of *Toxoplasma* neutralization tests in cases of chorioretinitis, noted that neutralizing bodies may be demonstrated in 10 to 14 per cent of persons who present



Residual isles of vision. Visual acuity was 3/60 for the left eye and 2/60 for the right eye. The perimetric fields were taken with a 17 mm test object at 330 mm.

no clinical manifestations of toxoplasmosis. However, as judged from Heidelman's conclusions and from those of other workers in the field, the neutralization test does seem to possess a fair degree of reliability. In the case reported here it may be considered as pointing to a possible cause of the inflammatory reaction in the choroid and in the brain. To account for disturbed pupillary reflexes and disjunctive nystagmus the lesion in the brain would be expected to involve the midbrain and pons. Attempting to name the implicated fiber bundles at present leads into the field of speculation.

Mayo Clinic

² Heidelman, J. M. Evaluation of *Toxoplasma* Neutralization Tests in Cases of Chorioretinitis, *Arch Ophth* 34:28-39 (July) 1945.

Correspondence

CYLINDRIC LENSES

To the Editor —With regard to the power of a cylindric lens, Duke-Elder (The Practice of Refraction, Philadelphia, P. Blakiston's Son & Co 1938, pp 274-275) draws attention to the work of Chalmers and Percival in explaining the error introduced in glasses used by the nonpresbyopic patient for distance and near work and points out that the practical importance of these facts lies in cases of high cylindric corrections in which if a $+5.00$ D cylinder is required for distance a $+5.5$ D cylinder is required for near work. As to the axis of the cylinder, in case of the torsional deviations of cyclophoria, at least, as has been known since the writings of Maddox, Stevens and Savage, rotation of the axis at the near point will neutralize the cyclophoric extorsion induced by convergence and may give clearer vision.

Further, Laurance and Wood (Visual Optics and Sight Testing, ed 4, London, The School of Optics, Ltd, 1936) stated years ago, in discussing the effectivity of cylindric lenses

- (a) A certain cylinder at a certain distance from the eye corrects more astigmatism if convex and less astigmatism if concave than its dioptric number indicates
- (b) a certain degree of astigmatism in the principal plane needs a weaker plus, or stronger minus cylinder when at a distance from the eye
- (c) the astigmatic effect of a given cylinder differs with the power of the sphere with which it is combined
- (d) its effect differs with the nearness of the object

They further stated (pages 342 to 343)

The whole subject resolves itself in calculation of the effectivities of the two principal powers, as with a spherical. The differences in the effective power when light is divergent are precisely the same as with sphericals. A cylinder, whether $+$ or $-$, which corrects a given degree of As for distance, no longer corrects it in near vision.

The change in effect is relatively greater as the lens is strong, that is to say, the higher power cx loses more of its effectivity, from the divergence of the light, than does the lower cx, the higher cc increases less than does the lower cc. There is less cylindrical effect in near than in distant vision in all cases.

The question of the effective values of cylindricals is further complicated by their combination with sphericals, and again with different sphericals for distance and close work.

These differences are by no means negligible from the point of view of comfort and visual acuity, and there is no doubt that adjustment of the cyls for near is indicated in such cases of high error if some reliable test were available, which, with the possible exception of dynamic retinoscopy, unfortunately is not the case.

Since, however, such strong corrections are rare, the changes in effect for near are generally negligible. This holds good because a cyl correction for near would be an over-correction for distance.

It was with surprise, therefore, that I noticed in a recent issue of the ARCHIVES the following statement by Dr Arthur Linksz, of Hanover, N H, in discussion on a paper by Dr Joseph I Pascal (Efficiency of

the Lens A Clinical Concept, ARCH OPHTH 34:466 [Nov-Dec] 1945) "About a year ago Dr Pascal himself added to knowledge in this field, demonstrating that the effectivity of an astigmatic correction is, for intrinsic reasons, different for near and for distant vision"

Dr Linksz is referring, I suppose, to comments by Dr Pascal published under "Correspondence" (The Axis in Astigmatism, ARCH OPHTH 27:489 [Jan] 1942) and to a later paper (Intrinsic Variability of Astigmatic Errors, ARCH OPHTH 32:123 [Aug] 1944) "I have reread these papers with interest and pleasure (believing, with Dr Pascal, that insufficient space is given to articles on refractive procedure in ophthalmologic journals), but the rereading did not disclose to me that in either paper Dr Pascal laid claim to originality for the facts in his presentations, as asserted by Dr Linksz"

These facts, indeed, were known to Badal, Young and others who studied the principles of the optometer and have been familiar to generations of men interested in the science of optics. A restatement in journals of previously known facts is often a worth while procedure. To infer, however, that this restatement enlarges the boundaries of scientific knowledge is incorrect. This note should not be construed as criticism of Dr Pascal, whose papers, spiced with optical wisdom and possessing a distinct didactic value, are a pleasure to read.

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SENILE HYALINE SCLERAL PLAQUES

To the Editor —Dr Kenneth L Roper's paper entitled "Senile Hyaline Scleral Plaques" (ARCH OPHTH 34:283 [Oct] 1945) has enhanced the meager knowledge of diseases of the sclera. Unfortunately, in his section on differential diagnosis no mention is made of ochronosis.

I observed a 78 year old man with bilateral "mesial" plaques while preparing my paper on "Ochronosis of the Sclera and Cornea" (*Tr Sect Ophth, A M A*, 1942, pp 66-96). The site and color of the two conditions are similar, in fact, Dr Roper's colored plate shows the slate blue of the ochronotic patch better than does the slate purple in my drawings. Younger ophthalmologists viewing our illustrations would have difficulty in distinguishing the two diseases. The association, however, of alkaptonuria, osteoarthritis and pigmentation of the ears and scleras establishes the diagnosis of ochronosis.

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Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

Bacteriology and Serology

BACTERIOLOGICAL AND CLINICAL OBSERVATIONS ON THE TREATMENT OF ACUTE OPHTHALMIAS OF EGYPT WITH SULPHONAMIDES AND PENICILLIN J O W BLAND and R P WILSON, Brit J Ophth 29: 339 (July) 1945

The effect of various doses of sulfapyridine, sulfathiazole, sulfadiazine and penicillin on the bacterial condition of the conjunctiva was studied by means of repeated examinations of smears in cases of the acute epidemic ophthalmias (due to the Koch-Weeks bacillus and the gonococcus) of Egypt

A single dose of a sulfonamide compound will cause a reduction of bacteria in four hours and total suppression of the organisms in about twelve hours. In a considerable proportion of cases of gonococccic ophthalmia cure will be effected with a single dose, but the form due to the Koch-Weeks bacillus is more resistant. Two doses of sulfathiazole or sulfadiazine given at eight hour intervals in one day will cure gonococccic ophthalmia in almost all cases but will not cure Koch-Weeks type in every case. Two doses on two successive days (four doses in all) will cure gonococccic ophthalmia and the type due to the Koch-Weeks bacillus in all cases, with rare exceptions.

A single intramuscular dose of penicillin will reduce the gonococci to zero in three to four hours, but repeated doses at short intervals are necessary to insure cure. Relapses occur in ten to twelve hours after a single dose. Penicillin has no effect on the Koch-Weeks bacillus and is therefore unsuitable in treatment of acute Egyptian ophthalmia.

W ZENTMAYER

Conjunctiva

TUBERCULOSIS OF THE CONJUNCTIVA C WESKAMP and J M VILA ORTIZ, An argent de oftal 5: 39 (April-June) 1944

The authors present a case of tuberculosis of the conjunctiva as a primary infection. The diagnosis was verified by histopathologic examination and the detection of the tubercle bacillus in the affected tissue.

The disease occurred in a youth 18 years of age who had no tuberculous antecedents and who was otherwise physically sound. The right upper lid was thickened. On eversion of the lid, the palpebral conjunctiva was found to be thickened, and papillomatous formations were present on the upper margin of the tarsus, with sessile tumefactions having a smooth, bright surface of a uniform red color, among which small, irregular ulcerations located on infiltrated tissue were seen. The rest of the eye presented nothing abnormal. The left eye was

normal There were enlarged preauricular lymph nodes and a small chain of enlarged cervical nodes The article is illustrated

H F CARRASQUILLO

Congenital Anomalies

CHOROIDEREMIA J GOEDBLOED *Ophthalmologica* 104.308 (Dec) 1942

Goedbloed states that in patients with choroideremia the external examination of the eyes does not reveal anything abnormal The media are clear The characteristic alterations are found in the background of both eyes With the exception of the optic disk and the region of the macula, the whole fundus shows a grayish or greenish white color which gives the impression almost of absence of the pigment layer of the retina and the choroid The term "choroideremia" is probably a misnomer, but it is impossible to say so definitely because of the complete lack of histologic information about this rare condition, of which only 34 cases have been reported in the literature The author discovered this condition in a man aged 38 He had the opportunity of subjecting to ophthalmologic examination also the patient's mother and only sister, the condition of whose fundi is best characterized as of the syphilitic pepper and salt type Discussing the hereditary transmission of choroideremia, the author reviews some reports from the literature, particularly that of Schutzbach, who in a family that could be followed for four generations detected 3 cases of choroideremia and several cases of a fundus condition that closely resembled the syphilitic pepper and salt type, although the Wassermann reaction of the blood in all cases was negative This picture was identical with that found in Goedbloed's female patients He concludes that choroideremia has an intermediate gonosomal (sex-linked) heredity . J A M A (W ZENTMAYER)

Cornea and Sclera

KERATOCONUS ITS DIAGNOSIS AND TREATMENT M I GREEN, Arch Asoc para evit ceguera en México 2:27, 1944

Green discusses fully the etiology, pathology, symptomatology, diagnosis and treatment of keratoconus He has observed 217 cases, 3 of which he describes One, that of a woman aged 26, another of a patient aged 24 and another of a patient aged 20 years Vision in these cases was much improved by the method of treatment employed, which was medical, surgical and refractive

He gives the following summary and conclusions "It is my opinion that in keratoconus one is dealing with a debilitated cornea which is unable to withstand the normal intraocular tension, in other words, a tension which is relatively high In its beginning the presence of this disease is generally not noticed When the diagnosis of keratoconus is established, medical treatment and a thorough periodic ocular examination are indicated If, in spite of the medical treatment, the disease progresses, a trephine operation combined with external canthoplasty should be performed Besides, general medical treatment, includ-

ing administration of vitamins (vitamin A and D and riboflavin) and use of contact lenses, should be prescribed

H F CARRASQUILLO

PATHOGENESIS OF PUNCTATE KERATITIS ASSOCIATED WITH ONCHOCERCOSIS A T ESTRADA, Arch Asoc para evit ceguera México 2: 63, 1944

Estrada has made biomicroscopic studies of the cornea in cases of onchocercosis of the eye. His observations were in cases of early infection in which extreme photophobia and ocular irritability are the characteristic symptoms and numerous microfilarias are found in the globe. Using diaphanoscopy and looking at the parallelepiped, he saw in the substantia propria elongated and rodlike, refringent structures, which he assumed to be bodies of dead parasites, surrounded by areas of punctate keratitis. He points out that the areas of deep-seated punctate keratitis were not accompanied with deep vascularization, as occurs in similar lesions of syphilis or tuberculosis.

H F CARRASQUILLO

Injuries

DOUBLE PERFORATION OF THE EYEBALL BY A FOREIGN BODY D M DEAN GUEL BENZU, Arch Soc oftal hispano-am 4: 381 (May-June) 1944

A case of double perforation of the globe by a foreign body is presented. The diagnosis was established by ophthalmoscopic and roentgenographic examinations. Eight days later, when the patient was to be discharged, with vision of 1, infection took place, and severe iridocyclitis developed. This was treated with subconjunctival auto-hemotherapy (1 cc of blood was injected), induction of mydriasis and local application of heat. A few days later the patient was discharged, with vision of 1.

H F CARRASQUILLO

Instruments

A RETINOMETRIC LOUPE OLIVERES, Arch Soc oftal hispano-am 4: 96 (Jan-Feb) 1944

The author has constructed a loupe with which measurements of the distances can be readily made. A 15 D loupe is formed by two plano-convex lenses cemented with Canada balsam. On the plane surface of one of these lenses a quadricle is engraved, the sides of each of the squares measuring 5 mm.

With the indirect method of ophthalmoscopy the quadricle is seen with the retinal image. The size of the optic disk being known and the number of the squares it covers, it is easy to determine the size and location of any retinal lesion.

H F CARRASQUILLO

Lacrimal Apparatus

MYCOTIC LACRIMAL CANALICULITIS R F PEREIRA, Arch de oftal de Buenos Aires 19: 410 (Oct) 1944

In seventeen years the author has seen 5 cases of this rare condition and has had the opportunity to study 3 of them carefully. In 1 case

the disease was bilateral. In all cases the os of the canaliculus was enlarged and partially dilated. Together with a bacterial flora of staphylococci, streptococci, diplococci, the Koch-Weeks bacillus and *Corynebacterium xerose*, a blastospore fungus was detected on culture. This fungus was classified as belonging to the subfamily *Microtorula* (genus *Candida*).

The 3 cases are described in detail.

The advantage of the surgical treatment by incision of the canaliculus is stressed.

H. F. CARRASQUILLO

Ocular Muscles

CONGENITAL PARALYSIS OF THE EXTERNAL RECTUS MUSCLE (DUANE'S SYNDROME) C. PAIVA, *Rev. brasil. de oftal.* 3: 25 (Sept.) 1944

This rare anomaly was first described in 1905 by Duane and is characterized by lessening or absence of external rotation of one or both eyes. It is caused by paralysis, usually partial, of the external rectus muscle and paresis of the internal rectus muscle, associated with a variable degree of retrocession of the globe and narrowing of the palpebral fissure during the movements of adduction or abduction. The patient shows no diplopia when looking straight ahead, although in some cases the head is turned slightly to the opposite side (ocular torticollis).

The clinical picture is not always the same but varies exceedingly, as can be seen from Adrogué's classification, presented in 1926. However, one symptom which characterizes this anomaly is present in every case, and that is the deficiency or congenital absence of abduction.

The cause is controversial. Some authors believe that the anomaly is due to the congenital absence of the external rectus muscle, others oppose this theory on the grounds that the lesion of the external rectus is always partial, while aplasia of the external rectus can be present without the enophthalmos which is always noted in cases of Duane's syndrome.

Diagnosis is made on the basis of objective and subjective data and of the anamnesis. The condition is easily diagnosed in the cases of unilateral retraction but is difficult to distinguish from a fixed alternating strabismus when it is bilateral. Differential diagnosis should be made between Duane's syndrome and functional strabismus or acquired paralytic strabismus of the sixth pair of cranial nerves.

Surgical treatment of this anomaly has been attempted but is generally unsuccessful. Some authors believe that an operation should be performed only when strabismus is present, and only then for the cosmetic effect.

The author presents one personal observation. A bibliography is included.

M. E. ALVARO

Retina and Optic Nerve

NEURORETINITIS AND MACULAR STAR E. CAMPOS, *Arq. brasil. de oftal.* 5: 131 (June) 1942

A patient 11 years of age had lost the sight of the right eye twelve days before examination. The conjunctiva, cornea and iris were normal. Isocoria was present. Vision was reduced to light perception, without

light projection. A perfect macular star and pronounced edema of the disk were present. Small hemorrhagic foci were seen in the region of the edema. The patient's parents were syphilitic, as he showed physical stigmas of hereditary syphilis, although no evidence was obtained from the laboratory tests, a diagnosis of neuroretinitis with macular star, possibly of syphilitic origin, was made. The literature dealing with such cases is reviewed. A bibliography is included.

M. E. ALVARO

RETROBULBAR NEURITIS IN CHENG TU PEI-CHING TANG, Chinese
M. J. 63:83 (Jan) 1945

A study was made of 52 cases of retrobulbar neuritis. The causative factors were chronic tonsillitis (19.2 per cent), sinusitis (5.4 per cent), tuberculosis (1.9 per cent), syphilis (1.9 per cent), dietary insufficiency (1.9 per cent) and dental infection (1.9 per cent). In 57.7 per cent no general symptoms of importance were elicited, and the exact etiologic factor remained obscure. In China, except for 1 suspected case of multiple sclerosis (Chow), retrobulbar neuritis associated with multiple sclerosis has not been reported. Most authorities agree that multiple sclerosis is rarely seen in China.

W. ZENTMAYER

Vision

AN EVALUATION OF VISUAL-ACUITY SYMBOLS W. S. FINK, Am. J. Ophth. 28:701 (July) 1945

Fink remarks the inaccuracy of present methods of measuring visual acuity. He discusses these various methods and concludes that the double broken circle of Ferree and Rand is the most practical of all symbols for patients over 7 and that the symbol E, or the triple break Landolt circle, is best for patients under 7 years of age. He feels that ophthalmologists should adopt a standard method and publicize the importance of the test.

W. S. REESE

ANISEIKONIA AND SPATIAL ORIENTATION H. M. BURIAN and K. N. OGLE, Am. J. Ophth. 28:735 (July) 1945

Burian and Ogle conclude that meridional aniseikonia always entails some type of incorrect spatial localization, which cannot be compensated. For the most part, these effects on spatial orientation are not perceived, since everyday surroundings offer unocular clues which dominate the bilateral data and rectify the incorrect spatial relationship of objects that would result from bilateral data alone.

W. S. REESE

Therapeutics

THE USE OF ARTIFICIAL-FEVER THERAPY IN OPHTHALMOLOGY I. C. SMITH and G. C. STRUBLE, Am. J. Ophth. 28:461 (May) 1945

Artificial fever therapy is a safe and certain method of treatment, with which therapeutic elevations of temperature can be easily attained, with a minimum of discomfort to the patient. It has many advantages over the use of triple typhoid vaccine. In ophthalmic practice excellent results

have been attained with treatment periods of not over two hours with an induced temperature of 105 F. When available, it should be considered the method of choice in treatment of those diseases of the eye for which adequate and repeated fever therapy may be a sight-saving measure.

W S REESE

CLINICAL EFFECTS OF THE LOCAL USE OF SULFONAMIDES ON THE EYES M E ALVARO, *Am J Ophth* 28 497 (May) 1945

Alvaro concludes that since sulfonamide compounds are almost innocuous to the ocular tissues, penetrate easily and act effectively, their topical application will largely supplant oral administration. He discusses their use, therapeutic indications and methods of administration.

W S REESE

News and Notes

EDITED BY DR W L BENEDICT

UNIVERSITY NEWS

Postgraduate Lectures in Ophthalmology—Meetings will be held in the department of ophthalmology, University of Glasgow, on Wednesdays during April and May at 8 p. m. The following papers will be read:

- April 3 "Industrial Ophthalmology," by Prof W J B Riddell
- April 10 "Keratoconjunctivitis," by Dr I C Michaelson
- April 17 "Concussion Injuries of the Retina," by Dr A M Wright Thompson
- April 24 "Ocular Tuberculosis," by Prof Arnold Loewenstem
- May 1 "Ocular Vitamin Deficiency," by Dr J D Fraser
- May 8 "Capillary Fragility," by Dr H N Munro

Discussion will follow the reading of the papers. The meetings will be open to all medical practitioners and senior students interested in ophthalmology.

Society Transactions

EDITED BY DR W L BENEDICT

CANADIAN OPHTHALMOLOGICAL SOCIETY

W G FRASER, M D, *President*

KENNETH B JOHNSTON, M D, *Secretary*

Seventh Annual Meeting, Montreal, June 15, 1945

Study of Visual Fields with the Tangent Screen DR J E PELLETIER, Quebec, Canada

The study of visual fields in the practice of ophthalmology is of great importance. It is helpful in the diagnosis and prognosis of many nervous, intracranial, traumatic and vascular conditions. Knowledge of the anatomy and physiology of the optic pathway is important, but one must not neglect the methods and technics of performing properly the investigation of the visual defects. Among these devices available are the perimeter and the tangent screen. The perimeter is the best means of studying the peripheral field up to 28 degrees from the fixation point. If one wants to investigate the quality of the defects of central and paracentral vision, it is best to use the tangent screen.

With the aid of the tangent screen one may easily study central, paracentral and pericentral scotomas. One may also find their exact location and dimensions. The significance of enlargement of the blindspot in the diagnosis of glaucoma and pathologic conditions of the optic nerve is itself sufficient reason for use of the tangent screen.

Thirty-three slides from illustrative cases of defects of the visual fields were shown.

DISCUSSION

DR COLIN A CAMPBELL, Toronto, Canada. With the tangent screen alone one may fail to note the contraction of the peripheral field in cases of glaucoma. There has been a tendency to neglect the perimeter. I strongly recommend the perimeter for determination of the peripheral fields. One can also use the perimeter to map out scotomas. I like to employ a round bead as a test object.

WING COMMANDER J V V NICHOLLS. I think the perimeter and the tangent screen should be used together.

DR J E PELLETIER, Quebec, Canada. One sometimes has to use both the perimeter and the tangent screen. The tangent screen is more logical for studies of the central field.

Causes of Blindness in over 12,000 Persons in Canada. DR F A AYLESWORTH, Toronto, Canada

In this study, data on 12,652 blind persons in Canada have been coded in accordance with the standard classification of the Committee

on Statistics of the Blind Information was obtained from the ophthalmologist's report on file at the Canadian National Institute for the Blind

In this blind population, vision varied up to 6/60, the upper limit accepted by the pension authorities In Canada 6,777 persons receive pensions

Of the diseases, glaucoma was the cause of blindness in the largest group of cases and myopia in the second largest Congenital anomalies, represented by a large third group, were classified together when reported as present at birth

In the large group of cases of blindness due to corneal conditions, corneal scars from infection or trauma were most common There were 104 cases of interstitial keratitis, a disease which should now be preventable Under diseases of the uveal tract, 299 cases of sympathetic ophthalmia were reported, a sharp reminder for ophthalmologists to attend to injuries of the eyes Retinitis pigmentosa accounted for 438 cases, in 100 of these there was a family history sufficient to prove that heredity was the cause of blindness Of 2,006 cases of disease of the optic nerve, the condition in 1,864 was due to atrophy of the optic nerve, in 56 to Leber's disease (hereditary optic atrophy) and in 62 to retrobulbar neuritis and in 24 cases it was due to disease of the higher visual centers Cataract as a cause of blindness was recorded in 3,124 cases, in 2,043 of which it was of senile type

The largest number of cases of blindness occur between the ages of 40 and 60, and the next largest past the age of 60 In World War I there was 1 blinded soldier in 1,235 casualties, in World War II, at the time of this report, the ratio was 1 1,400

From this review, one sees that a great deal of blindness is preventable I suggest examination of every person between the ages of 40 and 60, with cycloplegia, particularly for a critical view of the fundus and as a means of discovering incipient glaucoma This is the age at which routine examination can make a considerable contribution to the program of prevention of blindness

Three tables of classification of blindness accompanied the paper

DISCUSSION

DR W G M BYERS, Montreal, Canada In an examination, with Dr Brault and Dr Gelnas, of the blind at the Nazareth Institute, in Montreal, we were struck by the high percentage of congenital anomalies among the blind in the province of Quebec There arises the thought of compulsory sterilization in cases of diseases such as retinitis pigmentosa, in which the parents fully recognize the hereditary nature of the disease

• DR G A STUART RAMSEY, Montreal, Canada If a patient refuses operation for cataract, is he given a pension for the blind, or is he compelled to have treatment? A great many persons prefer to remain blind than to run the risk of an operation

DR ALEXANDER E MACDONALD, Toronto, Canada Dr Aylesworth's statistics are most complete Anything that can be done to help the Canadian National Institute for the Blind in compiling these statistics should be done

DR W G FRASER, Ottawa, Ontario Canada Some persons do refuse to have an operation for cataract I suggest that one of the patients who has had a successful operation be sent into the country for these people to see, I think they will often be convinced

DR F A AYLESWORTH, Toronto, Canada If we ophthalmologists cooperate with the Canadian National Institute for the Blind, many of these blind people will be assisted in transportation and arrangements for treatment

Pathologic Changes in the Retina Accompanying Tay-Sachs Disease

DR J A MACMILLAN, Montreal, Canada

A table was constructed showing the conditions in which lipid degeneration of the ganglion cells of the retina is found The infantile type of amaurotic familial idiocy, or Tay-Sachs disease, occurs at the age of about 6 months It shows a cherry red spot, found, with few exceptions, in the Jewish race alone, and in females in the ratio of 3:1 The late infantile type, described by Bielschowsky, occurs at the age of 3 to 5 years Usually there is no cherry red spot, but pigmentary changes in the macular region are seen It is nonracial in incidence The juvenile type, also known as Batten-Mayou, Spielmeier-Vogt or Spielmeier-Stock disease, and named by Oatman familial maculocerebral degeneration, occurs at the age of second dentition There are pigmentary changes in the macular region It is also nonracial Niemann-Pick disease, or lipid splenohepatomegaly, or lipid histiocytosis, which involves many structures in the body, may produce the typical ganglion cell changes in the retina A congenital type was described by Norman and Wood, and an adult type, by Kufs As Christian-Schuller and Gaucher disease do not affect the ganglion cells of the retina, they were not included in the table Wernicke, up to 1938, stated that the eyes of only 12 patients with Tay-Sachs disease had been examined microscopically

In the case here described, a Jewish boy died at the age of 17 months, with all the typical signs and symptoms of Tay-Sachs disease, including the gray area in the posterior pole and the cherry red spot in the macula Sections of the macula and the optic nerve were shown in lantern slides Various stains were employed including silver impregnations The ganglion cells were much reduced in number, and those remaining were greatly swollen and showed lipid deposits within the cell The nerve fiber layer was conspicuously reduced in thickness, but there still remained many fibers An interesting feature in this case was the presence in the deepest part of the bipolar cell layer of greatly swollen cells with round nuclei placed toward the periphery of the cell These cells resembled swollen ganglion cells, but of course they were far from the normal position of ganglion cells Again, they differed from microglia cells in the appearance of the cytoplasm and of the nuclei, so that one felt that they were bipolar cells which were filled with lipid material No change could be made out in the rods and cones The entire head of the optic nerve was rich in cellular content These cells were undoubtedly astrocytes and microglia cells Owing to the disappearance of many of the nerve fibers of the optic nerve and the degeneration of others, there was an apparent increase of connective tissue in the nerve, with spaces about the nerve bundles

The grayish white appearance of the posterior pole was due to the lipid in the ganglion cell layer of the retina. As the layer was absent in the macula, there was no disturbance in the reflection of light from the blood in the choroid, and the so-called cherry red spot was seen. It is suggested that in cases of the late infantile and juvenile types the cones are probably involved and that the pigmentary changes follow in the macular region, so that the cherry red spot is not visible.

Recession of the Inferior Oblique Muscle DR A LLOYD MORGAN, Toronto, Canada

The indications for lengthening the inferior oblique muscle were described.

Spasm of this muscle is usually secondary to palsy of the superior rectus muscle of the opposite eye. Various methods of lengthening the inferior oblique have been used at the Hospital for Sick Children, Toronto, for the last fifteen years. The operation giving the most consistent results has been recession of the muscle at the insertion.

The method is similar to that described by White. A double-armed 000 surgical gut suture is passed through the muscle twice and then through the sclera anterior to the insertion. The distance is determined by the amount of recession desired. The muscle is cut and allowed to recede. The exact technic was illustrated with lantern slides.

This paper will be published in full in the *Canadian Medical Association Journal*.

DISCUSSION

DR R E SMART, Ottawa, Ontario, Canada. In cases of bilateral superior rectus paresis my associates and I often do this type of work in stages, otherwise we get into trouble.

In double hyperphoria both eyes are too high. We bring one eye down in the first stage. Obviously, the patient looks worse when the bandage is removed.

Dr Morgan's technic varies slightly from ours in the placing of the sutures. I suggest that the first bite be taken into the sclera and then into the muscle. If the muscle is cut first, it is easily pulled forward.

DR H P FOLGER, Kingston, Ontario, Canada. One has to know how far to carry the recession of these muscles. In a recession of the inferior oblique my technic is the same as Dr Smart's, to place the sutures in the sclera first. I do not know how far back the recession of these muscles goes. I wish Dr Morgan would give a little more detail in this respect.

DR J A MACMILLAN, Montreal, Canada. In a few instances, while doing a resection of the external rectus, I have noticed a band of muscle fibers coming forward and upward and joining the external rectus muscle. It seemed to be a portion of the inferior oblique, but I can find no reference to this in the literature. Has Dr Morgan noticed these fibers in his operative work?

DR HENRI PICHETTE, Quebec, Canada. I like operating with local anesthesia.

DR A LLOYD MORGAN, Toronto, Canada With regard to placing the suture first in the muscle and then in the sclera and then cutting the muscle It can be done either in this way or as Dr Smart indicated, but the muscle should not be cut until the suture is in both the sclera and the muscle

I do not know how far to carry out the recession of the muscle, judgment comes with experience The results in the first cases were not particularly good I have not had an overcorrection One can usually do more than one thinks possible

Dr Pichette mentioned doing the operation with local anesthesia, I prefer a general anesthesia

O'Connor Advancement (Cinch) Operation. DR W G M BYERS, Montreal, Canada

O'Connor's advancement (cinch) operation was described and demonstrated This operation seems to be ideal for the correction of squints of low degree in children whose central and stereoscopic vision have been painstakingly developed and preserved by orthoptic training The postoperative freedom of movement, both general and ocular, permitted by this method is a boon because of the assurance and expedition with which orthoptic exercises, previously of no effect in reducing the angle of deviation, can be resumed, with frequent achievement of permanent parallelism in those cases in which coincident macular superimposition has followed operation

Since the tendon is not sectioned in the O'Connor operation, vertical and torsional effects are probably less common than with other types of advancement, and since, for the same reason, there is a minimum of interference with the integrity of the sensory nerve endings within the tendons of the ocular muscles, proprioceptive impulses continue to play their important role in the correlation of the ocular correspondences

The operation calls for a clean dissection and the minimum of trauma Dr Byers prefers a parallel incision in exposing the muscle because of the ease with which the ends of the cinching suture can be placed and fixed at the end of the operation

There has so far been displayed a proper conservatism in laying down precise estimates of the amount of correction of the deviation that can be achieved in relation to the essential steps of the procedure, but it may be that satisfying estimates of this kind will be obtained for a large group of patients selected in the light of complete preoperative orthoptic studies, as well as of precise measurements, after their exposure, of the length and breadth of the tendons involved

DISCUSSION

DR M R LEVEY, Edmonton, Alberta, Canada It is a little difficult to demonstrate the actual "cinch" operation in a diagram, and I am sure you will all be interested in looking at the apparatus Dr Byers has with him for the demonstration of this operation I always make sure I practice the technic the night before performing the operation

It is important that the terminal strands be placed in the right way In the majority of cases in which it was my privilege to assist Dr O'Connor, in 1938, he did a central tenotomy for the convergent strabismus However, I am not convinced that it was simply central I

find that I am much more satisfied when I do a recession. I have also found that one has to decide from experience how many muscle strands one should prepare, how many turns one should use and whether one loops over one, two or three times. That has to be gaged from experience.

Except in 1 case, I have had no postoperative inflammatory complications.

Relationship of Ocular Muscle Balance to Flying Performance SQUADRON LEADER L. S. S. KIRSCHBLRG, R C A F (by invitation)

This article will appear in full in a later issue of the ARCHIVES

DISCUSSION

DR A. LLOYD MORGAN, Toronto, Canada. I agree with Squadron Leader Kirschberg. The fact that glasses must be worn should not detract from one's being a good pilot. The air force has obtained a shatter-proof glass for aviators. I think I can say that members of the air crew can wear their shatter-proof glasses so long as their correction brings their vision down to normal.

DR E. A. McCUSKER, Regina, Saskatchewan, Canada. There are many men with the pullman idea. It was based on the standard of requirements established rather than on the young men examined.

MR. Bishop Harman asked me to provide men for trying out tests for night driving. He felt that many of the road accidents were due to the fact that some men should not be allowed to drive at night. Of 2,000 men examined, all had done considerable driving. Of all the men whom I had examined and pronounced absolutely unsuitable, I found none who had a record of accident, and all had been driving for days.

Clinical Aspects of Stereopsis. SQUADRON LEADER J. CLEMENT McCULLOCH, R C A F (by invitation)

This article will appear in full in a later issue of the ARCHIVES

DISCUSSION

DR W. G. M. BYERS, Montreal, Canada. I congratulate Dr McCulloch on his accurate investigation.

DR ALEXANDER E. MACDONALD, Toronto, Canada. If the paper is to be published, I would like to see it when it is available.

SQUADRON LEADER J. C. McCULLOCH. The paper will be published in conjunction with one by Squadron Leader Kirschberg in a future issue of the ARCHIVES OF OPHTHALMOLOGY.

Orthoptic Treatment of Convergence Insufficiency. DR CHARLES E. DAVIES, Vancouver, British Columbia, Canada

Convergence insufficiency is a weakening or failure of the normal ability of the eyes to maintain single binocular vision of any object with fusion at near working distance. It is primarily a failure of the autonomic and subvoluntary nervous systems with weakness of action of the fusion center in the brain. Reeducation and stimulation of the fusion center can be satisfactorily accomplished only by orthoptic training.

The symptoms are inability to concentrate at reading distance, photophobia, blurring of print, headaches, nausea and fatigue. The test is the ability of the patient to focus on an object as it approaches the eyes. Normal convergence is approximately 70 mm from the cornea. This test is repeated eight to twelve times. If the object recedes as the test is continued, this shows a poor convergence reserve. To test for suppression, the Worth four dot method is quick and accurate.

With orthoptic training a convergence reserve is created and central suppression can be corrected.

The Orthoptic Clinic in Vancouver was opened in 1939, with 1 orthoptist from Moorfields, London. Because of war conditions, my associates and I at the clinic found it necessary to train our own orthoptists. The students were university graduates and were given one year's course, the requirement laid down by the British Orthoptic Society.

The following instruments were found to be most useful, in the order of their importance: synoptophore, cheiroscope, rotoscope and diploscope.

After a careful refraction and elimination of all other causes, the patient is directed to the orthoptic clinic, where treatment is aimed at the cure of suppression, which often is alternating. Antisuppression exercises are followed by training for fusion and adduction. Before being discharged, the patient is able to converge voluntarily and involuntarily on an object brought up to a near point of 70 mm. Number of treatments vary from six to nineteen. A series of 150 consecutive cases of convergence insufficiency treated with orthoptic training were analyzed. In 70 per cent of these cases the result could be called a cure. Orthoptic training may not be the final answer, but it offers a scientific method of approach. Progress during the treatments can be checked with measurements on the synoptophore, exclusive of symptoms.

DISCUSSION

WING COMMANDER J. V. V. NICHOLLS: Certain of Dr. Davies' patients had pronounced suppression. I find it difficult to understand why a person who has suppression on convergence should have symptoms when working at near distance. I wonder how many of these patients have been seen by a psychiatrist.

DR. C. E. DAVIES, Vancouver, British Columbia, Canada: Until we can reduce suppression, we do not expect to get much in the way of results. I do refer the patients to the psychiatrist, but I get into trouble. They come back greatly annoyed that any one would think they were psychoneurotic. Most of them respond to synoptophore training. My impression is that more than half these patients have permanent improvement.

DR. COLIN A. CAMPBELL, Toronto, Canada: My colleagues and I have not got technicians to follow the long course of treatment. In the *British Medical Journal* 50 authors are for it and about 50 are indifferent. I have spent hours in training children for fusion. Some of the children keep on training, striving to get binocular vision. I think these children would have been better if I had not trained them. They had just enough training to give them diplopia. Children with this

type of insufficiency should not be trained, but only those with two good eyes. I do not think it necessary for children to have binocular vision as long as their eyes are straight.

DR KENNETH B. JOHNSTON, Montreal, Canada. What is the period of treatment for orthoptic training?

DR C. E. DAVIS, Vancouver, British Columbia, Canada. Patients cannot stand treatment for longer than five to ten months, and they come to the clinic at least twice a week. After the first or second week adults are able to take treatments for twenty minutes to half an hour. Later they are sent home with a machine and instructed to carry on their treatments at home. A number of them prefer orthoptic treatments to operation.

Book Reviews

El lente de contacto plastico. By Baudilio Coutis, M D , Julio N C Elola, M D , and Roberto Beltram Nunez, M D Pp 224, with 119 illustrations in black and white and colors Buenos Aires El Ateneo, 1945

The authors give the history of the contact lens from the time it was first used by J H Herschell, in 1827, to protect the globe from palpebral disease and its application by Fick, of Zurich, in 1888, in cases of keratoconus and ametropia, to the introduction of the molding procedure and of the plastic contact lens, which were developed chiefly by Oberg

The contact lens can be used for gonioscopy, for the correction of ametropias, especially in cases of optical keratoconus, for the correction of astigmatism after corneal transplantation, in cases of monocular aphakia, and for protection of the globe in cases of trichiasis, distichiasis, lagophthalmos and entropion

In its application, it is necessary to know the radius of curvature of the anterior 5 mm of the sclera, which fluctuates from 10 to 15 mm, and the diameter and radius of curvature of the cornea. Measurements obtained by molding show for the cornea an average of 12 mm for the vertical diameter and of 14 mm for the horizontal diameter, and a radius of curvature that varies from 7 to 5.8 mm

The authors discuss the mathematical theory of the contact lens and the possibility of correcting refractive errors either with the use of afocal lenses, by utilizing the liquid lens, or with addition of the correction to the contact lens

Different materials can be used to make the contact glass, though the most convenient are those derived from the acrylic acid derivatives, especially methyl methacrylate of resin, which is elastic, unbreakable and hard and has perfect transparency, with no selective absorption, and allows 92 per cent of the spectral light to pass through, with no interference for polarized light. Its weight is about 50 per cent less than glass, it is not altered by water, by the secretions of the tissues, by diluted alkalis or acids or by alcohol, and it is not toxic for the tissues and can be tinted

With respect to the liquid lens, several qualities of the liquids used must be taken into consideration, since the tolerance of the contact lens depends much on them, these qualities are the p_H , the osmotic pressure and the chemical composition, together with physical qualities, such as the refractive index, which ranges from 1.335 to 1.336, and the constancy of the fluids. The p_H could be kept constant with the use of "buffers," but the fluid must be renewed to preserve the osmotic pressure and the chemical composition. When these conditions are fulfilled, intolerance to the lens may still be due to faulty fitting. The changes in the composition of the liquid lens depend on the presence of a closed space and its interchanges with the cornea. The selection of the fluid is tedious and 90 per cent of the failures in the use of contact lenses

are due to the fluid in use. Various solutions have been used, but one of the best is a 2 per cent solution of sodium bicarbonate, it should be freshly made, and the prescription of 0.2 Gm. of the powder in 10 cc. of distilled water is recommended. When this fails, the use of a "buffer" is recommended. After four or five hours, which is the average time of tolerance, the lens should be removed, and it can then be reapplied after a lapse of one-half hour.

In examining a patient for contact glasses, molding can be eliminated in most cases by determining (1) the radius of curvature and the diameter of the cornea, (2) the radius of curvature of the sclera, (3) the correction for ametropia and (4) the vertex distance. A new trial case of contact lenses is suggested which contains 30 instead of 10 lenses, as in the one used by Obrig. The lenses have radii of curvature for the corneal segment of 6.5, 7, 7.5 and 8 mm. The radius of curvature for the scleral segment increases by 0.25 mm. and ranges from 2 to 3 for the first two and the last corneal curvatures designated and from 1.5 to 3 for the 7.5 mm. corneal curvature. These lenses determine the corneal and the scleral radius of curvature. The refraction of the patient is tested with the contact trial lens in and the distance from the correcting lens in the trial frame to the vertex of the contact trial lens is measured (vertex distance).

A prescription for a contact lens must include (1) the name of the patient, (2) the side of the eye, (3) the radius of curvature and diameter of the cornea, (4) the radius of curvature of the sclera in the different axes, (5) the optical correction and (6) vertex distance.

In the molding, two kinds of material are mainly used. Negocolle and Moldite, the latter dries faster while the former gives neater molds.

When the lenses have been finally made, the complaint is usually to be found in an ill fit of the contact lens. The authors stress the importance of displacement of the corneal segment and excessive pressure on the scleral segment. Areas of contact are uncovered with the use of fluorescein and examination with the slit lamp and the cobalt blue light.

The illustrations, many in color and in making this book a clear and practical exposition of the subject of contact glasses.

HUMBERTO ESCAPINI

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 Secretary Dr Tom Barr, Medical Arts Bldg, Dallas 1, Texas
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 from October to June The November, January and March meetings are
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 Place Club rooms of Wayne County Medical Society Time First Monday of
 each month, November to April, inclusive

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 Secretary Dr Arthur Hale, 1609 Eaton Tower, Detroit 26
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 Place Medical Arts Bldg, Harris County Medical Society Rooms Time 8 p m,
 second Thursday of each month from September to June

INDIANAPOLIS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr Myron Harding, 23 E Ohio St, Indianapolis
 Secretary Dr Kenneth L Craft, 23 E Ohio St, Indianapolis
 Place Indianapolis Athletic Club Time 6 30 p m, second Thursday of each
 month from November to May

KANSAS CITY SOCIETY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Edgar Johnson, 906 Grand Ave, Kansas City, Mo
 Secretary Dr W E Keith, 1103 Grand Ave, Kansas City, Mo
 Time Third Thursday of each month from October to June The November,
 January and March meetings are devoted to clinical work

LONG BEACH EYE, EAR, NOSE AND THROAT SOCIETY

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 Secretary-Treasurer Dr Robert G Thornburgh, 117 E 8th St, Long Beach, Calif
 Place Seaside Hospital Time Last Wednesday of each month from October to May

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

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 Secretary-Treasurer Dr K C Brandenburg, 110 Pine Ave, Long Beach 2, Calif.
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 6 30 p m, fourth Monday of each month from September to May, inclusive.

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 Secretary-Treasurer Dr J W Fish, 321 W Broadway, Louisville, Ky
 Place Brown Hotel Time 6 30 p m, second Thursday of each month from September to May, inclusive

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 Secretary Dr James J Monohan, 31 S Jardin St, Shenandoah, Pa

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 OPHTHALMOLOGY AND OTOLARYNGOLOGY

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 Secretary Dr Frazier Williams, 1801 I St N W, Washington
 Place 1718 M St N W Time 8 p m, third Friday of each month from October to April, inclusive

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Each member, in alphabetical order
 Secretary Dr Sam H Sanders, 1089 Madison Ave, Memphis, Tenn
 Place Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital Time 8 p m,
 second Tuesday of each month from September to May

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President Dr Ralph T Rank, 238 W Wisconsin Ave, Milwaukee
 Secretary-Treasurer Dr Frank G Treskow, 411 E Mason St, Milwaukee 2
 Place University Club Time 6 30 p m, fourth Tuesday of each month from October to May

MONTGOMERY COUNTY MEDICAL SOCIETY

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 Secretary-Treasurer Dr Matland D Place, 981 Reibold Bldg, Dayton, Ohio
 Place Van Cleve Hotel Time 6 30 p m, first Tuesday of each month from October to June, inclusive

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President Dr J Rosenbaum, 1396 Ste Catherine St W, Montreal, Canada
 Secretary Dr L Tessier, 1230 St Joseph Blvd E, Montreal, Canada
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NASHVILLE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Dr M M Cullom, 700 Church St, Nashville, Tenn
 Secretary Dr R E Sullivan, 432 Doctors Bldg, Nashville, Tenn
 Place James Robertson Hotel Time 6 30 p m, third Monday of each month from October to May

NEW HAVEN OPHTHALMOLOGICAL SOCIETY

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 Secretary Dr Frederick A Wiess, 255 Bradley St, New Haven, Conn

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 Secretary Dr Mercer G Lynch, 1018 Maison Blanche Bldg, New Orleans
 Place Louisiana State University Medical Bldg Time 8 p m second Tuesday
 of each month from October to May

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Chairman Dr Rudolf Aebli, 30 E 40th St, New York
 Secretary Dr Truman L Boyes, 654 Madison Ave, New York
 Time 8 30 p m, third Monday of every month from October to May, inclusive

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President Dr Maurice L Wieselthier, 1322 Union St, Brooklyn
 Secretary Dr Benjamin Esterman, 983 Park Ave, New York 28
 Place New York Academy of Medicine, 2 E 103d St Time 8 p m, first Monday
 of each month from October to May, inclusive

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 Secretary Dr S R Shaver, 117 N Broadway, Oklahoma City
 Place University Hospital Time Second Tuesday of each month from Sep-
 tember to May

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OTO-LARYNGOLOGICAL SOCIETY

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 Secretary-Treasurer Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha 2
 Place Omaha Club, 20th and Douglas Sts, Omaha Time 6 p m dinner, 7 p m
 program, third Wednesday of each month from October to May

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 Secretary-Treasurer Dr J Averbach, 435 Clinton Ave, Clinton, N J
 Place Paterson Eye and Ear Infirmary Time 9 p m, last Friday of every
 month, except June, July and August

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 Secretary Dr Glen Gregory Gibson, 255 S 17th St, Philadelphia
 Time First Thursday of each month from October to May

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President Dr Clarence F Bernatz, Park Bldg, Pittsburgh
 Secretary Dr Robert J Billings, Park Bldg, Pittsburgh
 Place Pittsburgh Academy of Medicine Bldg Time Fourth Monday of each
 month, except June, July, August and September

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President Dr Isaac B High, 326 N 5th St, Reading, Pa
 Secretary Dr Paul C Craig, 232 N 5th St, Reading, Pa
 Place Wyomissing Club Time 6 30 p m, third Wednesday of each month from
 September to July

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President Dr Luther C Brawner, Professional Bldg , Richmond, Va
 Secretary Dr Clifford A Folkes, Professional Bldg , Richmond, Va
 Place Westmoreland Club Time 6 p m , second Monday of each month from
 October to May

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President Dr Frank Barber, 75 S Fitzhugh St , Rochester, N Y
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ST LOUIS OPHTHALMIC SOCIETY

President Dr Vincent Jones, 634 N Grand Blvd , St Louis
 Secretary Dr T E Sanders, 508 N Grand Blvd , St Louis 3
 Place Oscar Johnson Institute Time Fourth Friday of each month from October
 to April, inclusive, except December, at 8 00 p m

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 Secretary-Treasurer Lt Col John L Matthews, AAF School of Aviation Medi-
 cine, Randolph Field, Texas
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 Aviation Cadet Center Time 7 p m , second Tuesday of each month from
 October to May

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Chairman Dr Roy H Parkinson, 870 Market St , San Francisco
 Secretary Dr A G Rawlins, 384 Post St , San Francisco
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 Tuesday of every month except June, July and December

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 Secretary-Treasurer Dr Kenneth Jones, Medical Arts Bldg , Shreveport, La
 Place Shreveport Charity Hospital Time 7 30 p m , first Monday of every
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President Dr Clarence A Veasey Sr , 421 W Riverside Ave , Spokane, Wash
 Secretary Dr Clarence A Veasey, 421 W Riverside Ave , Spokane, Wash
 Place Spokane Medical Library Time 8 p m , fourth Tuesday of each month
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President Dr A H Rubenstein, 713 E Genesee St , Syracuse, N Y
 Secretary-Treasurer Dr I H Blaisdell, 713 E Genesee St , Syracuse, N Y
 Place University Club Time First Tuesday of each month except June, July
 and August

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 Secretary Dr W W Randolph, 1838 Parkwood Ave , Toledo, Ohio
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Secretary Dr W T Gratton, 216 Medical Arts Bldg, Toronto, Canada

Place Academy of Medicine, 13 Queens Park Time First Monday of each month, November to April

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Secretary-Treasurer Dr Richard W Wilkinson, 1408 L St N W, Washington, D C

Place Medical Society of District of Columbia Bldg, 1718 M St N W, Washington, D C Time 7 30 p m, first Monday in November, January, March and May

WILKES-BARRE OPHTHALMOLOGICAL SOCIETY

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Secretary Dr Samuel T Buckman, 70 S Franklin St, Wilkes-Barre, Pa

Place Office of chairman Time Last Tuesday of each month from October to May

CORNEAL SECTION WITH LONG BEVEL AND CONJUNCTIVAL FLAP FOR CATARACT EXTRACTION

Preliminary Report

WALTER S ATKINSON, MD

WATERTOWN, N Y

IN CATARACT extraction complications that formerly occurred at the time of operation have been reduced to a minimum by better anesthesia and improved operative technic. Attention is now directed more toward the prevention of postoperative complications.

The principal aims of the corneal section to be described are to prevent a leaky wound, with a shallow or empty anterior chamber, and to

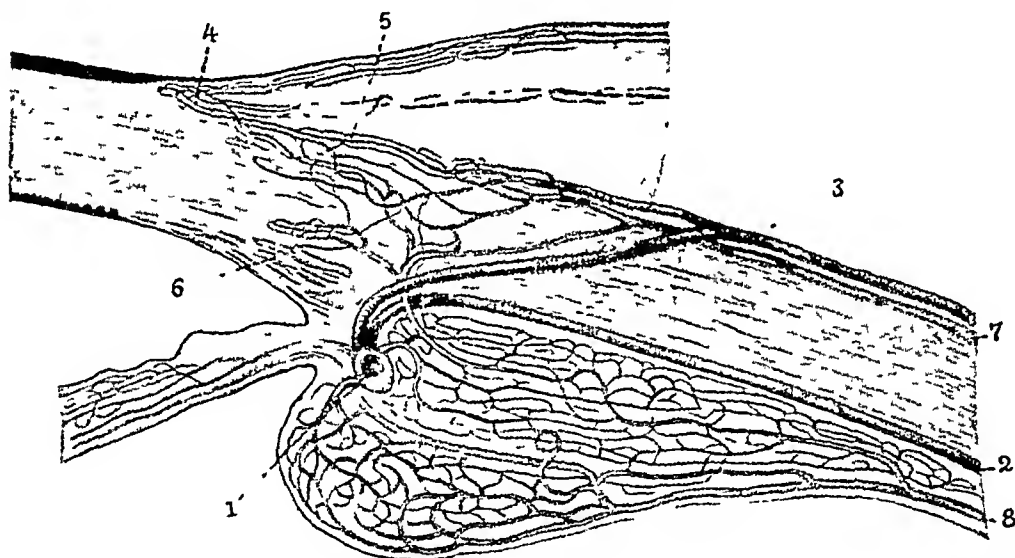


Fig 1—Blood vessels of the anterior segment (after Maggiore, L. *Ann. di ottol e clin ocul* 40 317, 1917)

decrease the occurrence of postoperative hemorrhage into the anterior chamber.

Two features of the section designed to accomplish these aims are (1) a long bevel and (2) placement in avascular corneal tissue.

Firm suturing of the wound has practically eliminated prolapse of the iris, but the closure of the wound is often not sufficiently perfect to prevent a slow leak of aqueous or to prevent blood from entering the anterior chamber. It is generally conceded that to be effective sutures

Read at the Eighty-First Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., Nov. 12, 1945. At the time of presentation 50 cases comprised group 3.

must be placed in firm corneal or corneoscleral tissue and that such sutures can be more safely introduced before the section is made. The principle of introducing the suture before making the section was first advocated over fifty years ago by Suarez de Mendoza¹ and Kalt². More recently, modifications by Liegard,³ Stallard,⁴ McLean⁵ and others have emphasized this point.

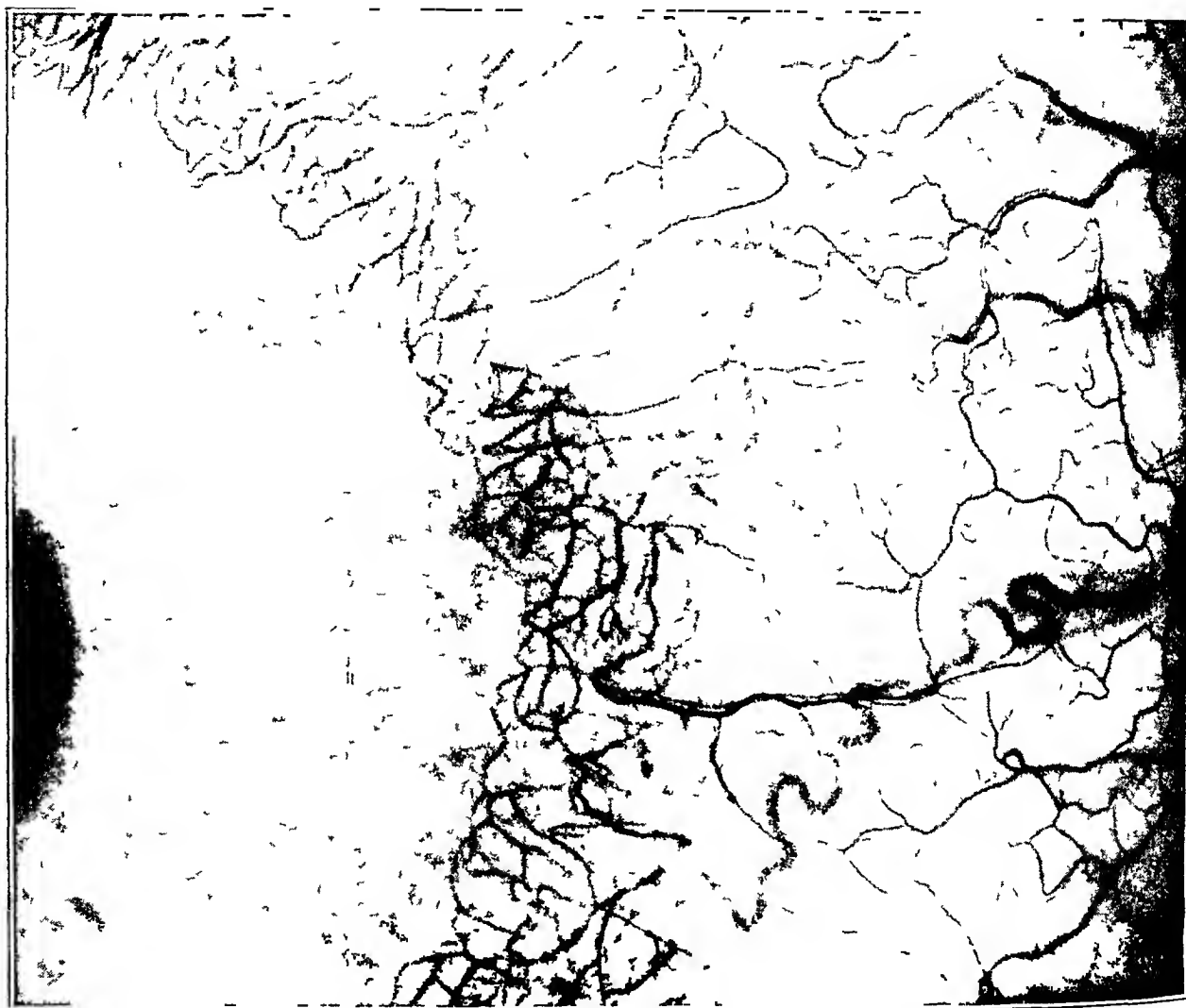


Fig 2—4, normal capillaries of the limbus *B* (on facing page), engorgement of deeper set of arteries and the limbal capillaries such as might occur after cataract extraction (from Gartner, S. Blood Vessels of the Conjunctiva, *ARCH OPHTH* 32 464 [Dec] 1944, figs 2 and 5)

1 Suarez de Mendoza, F. Nouveaux faits de suture de la corneé dans l'extraction de la cataracte, *Bull et mem Soc franç d'opht* 10 63, 1892

2 Kalt, E. On the Corneal Suture in Cataract Extraction, *Arch Ophth* 23 421, 1894

The McLean suture satisfactorily fulfils the requirements, and it is easy to introduce. The chief advantage of the McLean suture over the Kalt, Liégard or Stallard type is that with it there is no overriding or lateral displacement.

The section is particularly important because it greatly influences and governs postoperative complications. Section with the Graefe knife when perfectly performed thrills even the seasoned surgeon. The most experienced operators, however, are not always able to obtain a perfect

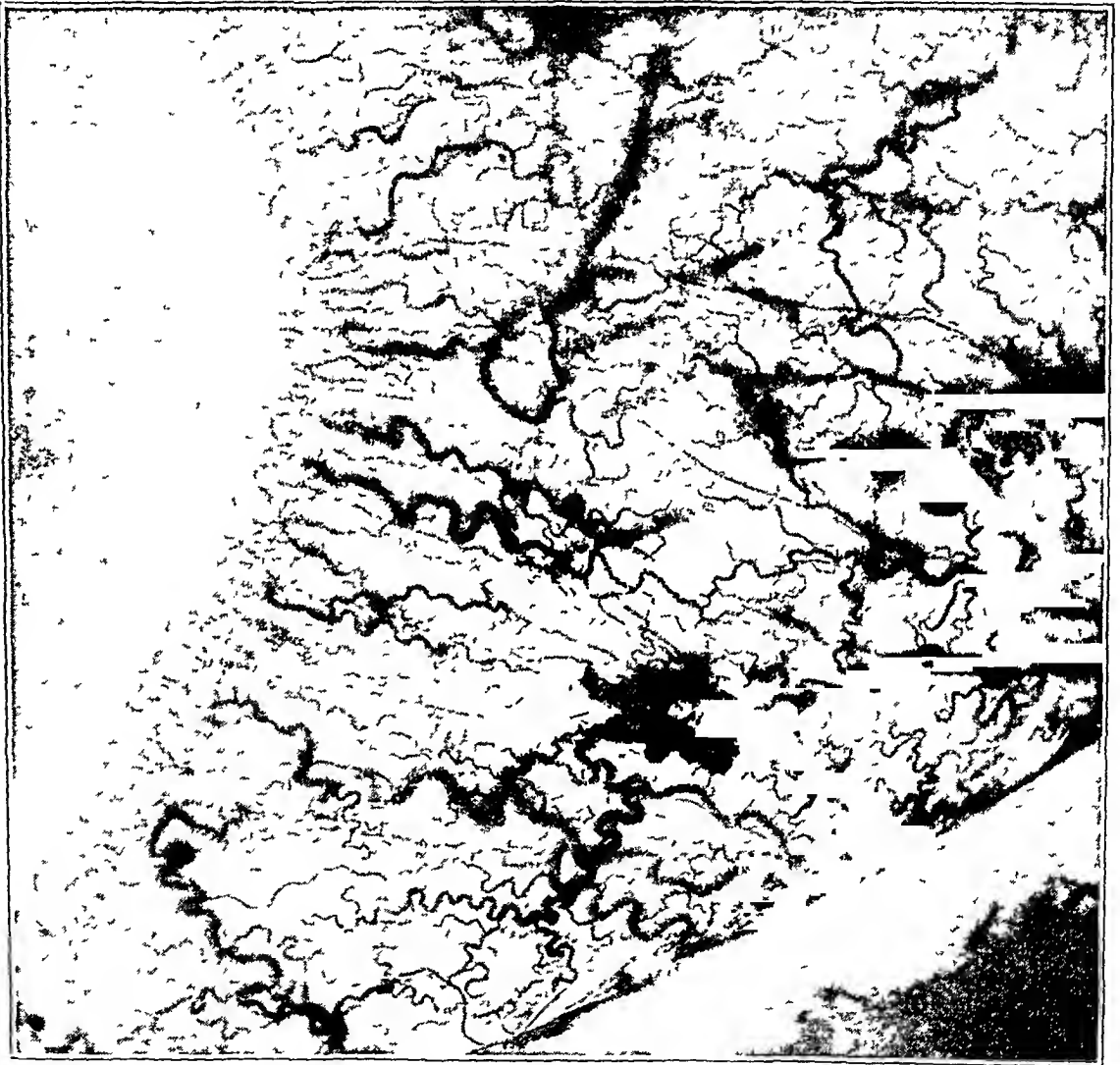


Figure 2 B

3 Liégard, H. Une modification au procédé de suture de la cornée dans l'extraction de la cataracte, *Ann d'ocul* **149** 119, 1913

4 Stallard, H. B. A Corneo-Scleral Suture in Cataract Extraction. Its Technique and Advantages, *Brit J Ophth* **22** 269, 1938

5 McLean, J. M. A New Corneoscleral Suture, *Arch Ophth*, **23** 554 (March) 1940

section with the Graefe knife. When the section is placed too far back, so that the vascular loops (fig 1) are cut, bleeding complicates not only the operation but the convalescence. If the Graefe section is placed too far forward, a satisfactory conjunctival flap is not obtained. The importance of a conjunctival flap is so generally conceded that comment is unnecessary.

A large section is essential in order to allow easy extraction of the cataractous lens without rupture of the capsule or undue trauma. To obtain a well placed section, with a Graefe knife, of one-half the circumference of the cornea without injury to the iris is not always possible, particularly if the anterior chamber is shallow. Therefore, many surgeons now prefer to make a small initial incision with the Graefe knife or keratome and to enlarge it with scissors.

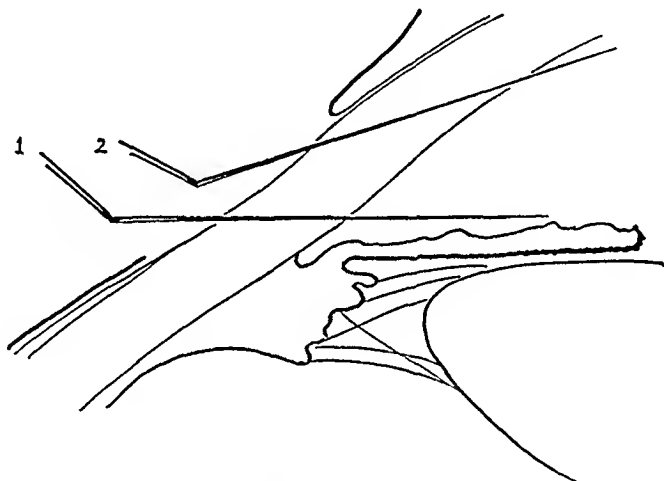


Fig 3—1, usual angle of keratome incision, 2, long bevel obtained when the point of the keratome is directed away from the iris and toward the apex of the cornea

Some of the advantages of the keratome for the initial incision have been pointed out by O'Brien⁶. An important point that O'Brien mentioned is that the section can be more easily and accurately placed.

Besides the advantages described by O'Brien, it is well known that the usual keratome incision is beveled, so that increased intraocular pressure tends to close the wound more tightly. If, therefore, the bevel is continued when enlarging the wound, a firmer closure is procured, so that the wound is less likely to leak. Although such a section with corneal ledge is contrary to orthodox teaching, it is the first point to be emphasized.

As shown diagrammatically in figure 3, if the point of the keratome is directed away from the iris and toward the apex of the cornea, the

6 O'Brien, C. S. Comparison of the Keratome-Scissors and Graefe Knife Incisions for Cataract Extraction, *Am J Ophth* 26:508, 1943

length of the bevel is increased. Such an incision tends to close more firmly and tightly when the normal intraocular pressure is restored or the intraocular pressure is increased. It should be noted, however, that with the long bevel placed well forward in the cornea it is essential to tumble the lens. Should the capsule rupture it is more difficult to express the lens matter, but since rupture of the capsule is not a frequent occurrence, it is not a serious consideration.

The hypermature cataract with a large, flat nucleus which does not tumble easily is more readily delivered head first, as suggested by Verhoeff.⁷ In cases of this type an incision with a shorter bevel may be placed farther back. The possibility of hemorrhage is increased, and the closure may not be so firm, but to remove the lens in capsule seems more important than the increased risk of postoperative hemorrhage or a leaky wound.

Considerable investigation and discussion have failed to determine definitely the source and cause of all hemorrhages that occur after cataract extraction. There is, however, good evidence that the majority are from the newly formed vessels that cross the surface of the wound. It is generally agreed that most of the hemorrhages occur on the fourth to the sixth day. Henderson⁸ and Collins⁹ showed that it is on these days that new blood vessels grow across the wound, and Worth¹⁰ pointed out that a slight rupture of the wound would tear the newly formed vessels. Vail¹¹ concurred in the opinion that the rupture of newly formed blood vessels at the section is the most frequent cause of hyphema. A thorough review of the literature by DeVoe¹² and careful analysis of 95 cases of hemorrhage into the anterior chamber following cataract extraction in a series of 453 cases support the contention that the rupture of vessels which cross the surface of the wound is responsible for a large share of the hemorrhages.

It seems logical to expect less bleeding if the wound is located in tissue in which there are fewer and smaller vessels to rupture. Since the conjunctiva is not firmly attached to the cornea in the periphery (fig 4), a flap can easily be made which exposes as much as 2 to 3 mm

7 Verhoeff, F. H. A New Operation for Removing Cataracts with Their Capsules, *Tr Am Ophth Soc* **25** 54, 1927

8 Henderson, T. A Histological Study of the Normal Healing of Wounds After Cataract Extraction, *Ophth Rev* **26** 127, 1907

9 Collins, T. Postoperative Complications of Cataract Extraction, *Tr Ophth Soc U Kingdom* **34** 41, 1914

10 Worth, C., in discussion on Collins,⁹ p 67

11 Vail, D. On Hyphema After Cataract Extraction, *Tr Am Ophth Soc* **31** 496, 1933, Hyphema After Cataract Extraction, *Am J Ophth* **24** 920, 1941

12 DeVoe, G. Hemorrhage After Cataract Extraction, *Arch Ophth* **28** 1069 (Dec) 1942

of cornea This allows the section to be placed well forward in the cornea, so that the vascular loops are avoided Placing the section in avascular corneal tissue is the second point to be emphasized

TECHNIC OF OPERATION

The technic of the corneal section with long bevel and conjunctival flap is as follows

To dilate the pupil, 4 per cent homatropine hydrobromide is instilled in the eye one hour before operation Anesthesia, as previously described,¹³ is produced by the instillation of 0.5 per cent tetracaine hydrochloride and several drops of epinephrine hydrochloride 1:1,000 Procaine hydrochloride, 2 per cent with

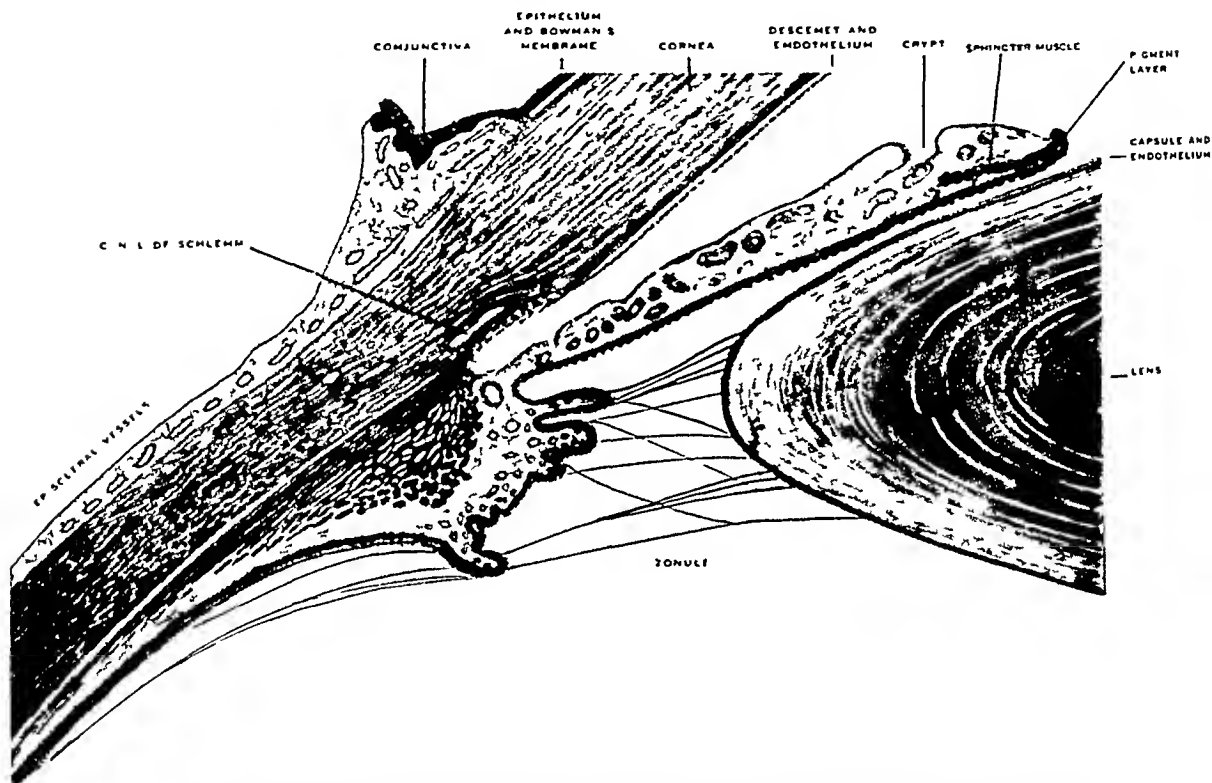


Fig 4—Loose attachment of the conjunctiva at the periphery of the cornea (from Wolff, E. The Anatomy of the Eye and Orbit, Philadelphia, The Blakiston Company, 1940)

epinephrine hydrochloride is used to produce akinesia and for the cone injection An injection of procaine is also made along the superior rectus muscle to avoid pain caused by the introduction of the suture in the superior rectus

To make the conjunctival flap, a snip is made in the conjunctiva with blunt-pointed scissors about 4 mm above the corneal margin The cut edge of the conjunctiva is picked up, care being taken to avoid the subconjunctival tissue The blade of the scissors is then slid under the conjunctiva, and a flap sufficiently

¹³ Atkinson, W S Local Anesthesia in Ophthalmology, Arch Ophth 30 777 (Dec) 1943

large to cover the wound is made. Little bleeding occurs if the subconjunctival tissue and the vessels are avoided. The thin conjunctival flap may be turned down over the cornea with practically no dissection. The conjunctiva is more firmly adherent temporally as the 180 degree meridian is approached, and not so much cornea is exposed, either temporally or nasally, as there is above. The amount of cornea exposed can be increased by a little dissection with scissors, knife or Green corneal splitter.

A McLean⁵ type of suture is introduced above at 12 o'clock. One suture is usually sufficient, but if more are indicated they may be introduced after the central one is tied. For the initial incision a straight-sided keratome, 4 to 5 mm wide (fig 5) is used. It is introduced at the site of the suture, and at an angle to produce a long bevel. The wound is enlarged with keratome as it enters the anterior chamber and as it is partially withdrawn and reintroduced with a sawing motion. No aqueous escapes as the keratome is introduced, so that several strokes can usually be made and the wound enlarged halfway to the 180 degree meridian.

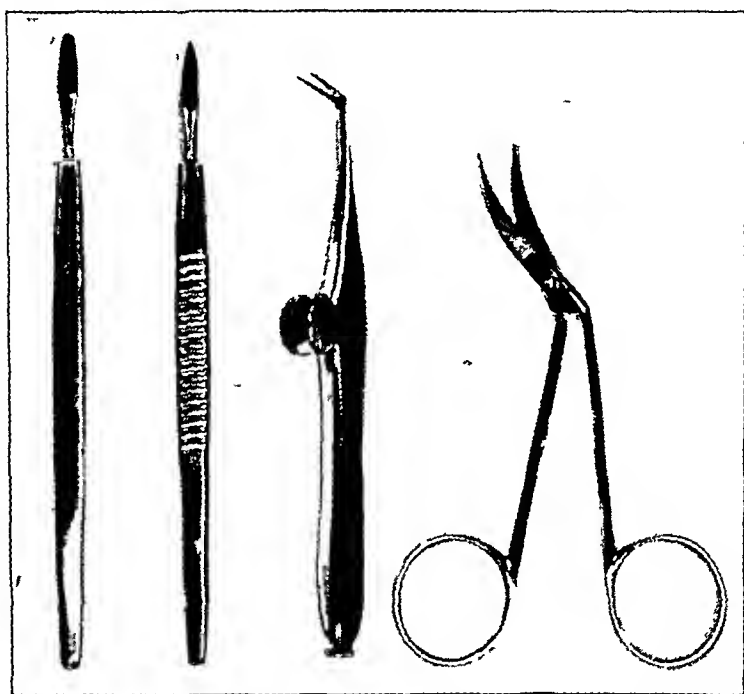


Fig 5—Left to right. Blunt-pointed keratome, straight-sided keratome, de Wecker scissors, both blades pointed, modified Walker scissors.

before the aqueous escapes. If the aqueous is lost, a blunt-pointed, straight-sided keratome (fig 5) is used to complete the enlargement of the wound because it can be introduced more easily and safely into a shallow or empty chamber. A straight-sided keratome is preferred because so little counterpressure is required to introduce it, aqueous is rarely lost and it makes a straight, linear cut. The longest bevel is made in the middle third of the section and extends from 10 30 to 1 30 o'clock, where prolapse of the iris and leaks most frequently occur. The wound is further enlarged with scissors to one-half the circumference of the cornea. The amount of bevel is decreased as the 180 degree meridian is approached because if the long bevel were continued to the 180 degree meridian the wound would not open widely enough to allow easy extraction of the lens. The bevel may be increased or decreased with scissors by tipping the inside blade toward or away from the cornea.

It should be noted that it is more difficult to begin the enlargement of the wound with scissors when there is a long bevel. If, however, the scissors are well opened, so that the blade that enters the anterior chamber clears the broad edge of the wound produced by the long bevel, little difficulty will be experienced. Short snips should be made with the scissors to avoid buckling the cornea. A modified Walker scissors (fig 5) has been found to be the most satisfactory in enlarging the wound.

In many instances, with the pupil dilated, the iris is practically covered above by the corneal ledge. If not, one to three iridotomies are made at 12 00, 10 30 and 1 30 o'clock, respectively, using de Wecker scissors which have the two blades pointed and of the same length (fig 5). The corneal flap is raised, the iris drawn down a little with the points of the scissors and a small hole snipped in the iris close to the upper corneal lip. No forceps are used to grasp the iris.

For immature or mature cataracts the anterior capsule is grasped well below with the Elschmig modification of the Kalt forceps, and the lens is tumbled and extracted with pressure and traction. The technic and method of extraction, however, are changed to suit the type of cataract encountered. The aim is to remove the cataract in capsule as safely as possible, regardless of the method or combination of methods used.

After the suture is tied and toilet of the wound completed, other sutures may be safely introduced if desired. The conjunctival flap is smoothed out but not sutured, and the anterior chamber is filled with half-normal saline solution or air.

A 0.25 per cent physostigmine salicylate ointment is instilled except when the iris is practically covered by the corneal shelf. In such cases atropine is used to keep the pupil dilated and the iris under the corneal shelf. When atropine is instilled at the completion of the operation, practically no postoperative pain is experienced. While the crampy pain which regularly occurs after the instillation of physostigmine is easily controlled, it is preferable not to have the pain.

EVALUATION OF TECHNIC

An analysis of cataract extractions done by different methods is given in order to evaluate the technic described.

A series of 300 cataract extractions is divided into three groups. In group 1 are 100 consecutive extractions in which a corneoscleral section with conjunctival flap was made with a Graefe knife. Corneoscleral sutures were introduced after the section. In group 2 are 100 consecutive extractions in which a conjunctival flap was first made. A Stallard type of suture was introduced before the section, which was made with a keratome and enlarged with scissors.

In group 3 are 100 consecutive extractions in which a conjunctival flap was first made. A McLean type of suture was introduced, and a long-beveled section was made with keratome and enlarged with keratome and scissors.

As the series progressed, more careful notes were made with regard to leaky wounds and blood in the anterior chamber. If the chamber was observed to be just a little shallow at one dressing, the case was recorded as one of a leaky wound. Any blood in the anterior chamber,

such as a small blood stain of the iris, was listed as hemorrhage in the anterior chamber. This may in a measure account for the comparatively small decrease in the number of leaky wounds and hemorrhages recorded in groups 2 and 3 as compared with the number in group 1, for in the first group such minor leaks and hemorrhages were not all recorded. Therefore the tables give an erroneous impression in regard to the leaks and hemorrhages, particularly in group 3. Actually, in group 3 there was only 1 empty chamber and 1 hemorrhage large enough to prolong the patient's stay in the hospital.

COMMENT

As shown in table 1, there were no serious complications due to leaky wounds in groups 2 and 3. In group 1 a leaky wound was a

TABLE 1—*Visual Results in 33 Cases With Leaky Wounds in a Series of 300 Cataract Extractions*

Visual Acuity	Group 1 (100 Cases)		Group 2 (100 Cases)		Group 3 (100 Cases)
20/15	5		8		2
20/20	5		2		3
20/25	5		1		4
20/200*	1	Detachment of retina			
10/200	1	Secondary glaucoma and diabetic retinopathy			
Total	17	17%	11	11%	9 9%

* Vision was 20/30 until detachment occurred, eleven months after operation.

serious complication in 2 cases. In 1 case vision was 20/30 until detachment of the retina occurred, eleven months later, after which it was reduced to 20/200. The leak was considered responsible for the

TABLE 2—*Visual Results in Cases of Hemorrhage in Anterior Chamber Which Occurred in a Series of 300 Consecutive Cataract Extractions*

Visual Acuity	Group 1 (100 Cases)		Group 2 (100 Cases)		Group 3 (100 Cases)
20/15	7		6		2
20/20	3		2		2
20/25	5		2		4
Died in hospital	0		1		0
Total number of cases with hyphemia	15	15%	11	11%	8 8%

detachment, because vitreous was pinched in the wound at the site where it opened. In the second case secondary glaucoma developed. A cyclodialysis controlled the intraocular pressure, but diabetic retinopathy was also present and accounted for some loss of vision, so that final vision was 10/200.

The visual results shown in table 2 indicate that hyphemia is not a serious complication. Vision was affected little, but convalescence in some instances was prolonged, so that several days were added to the stay in the hospital. In groups 2 and 3 all but 2 of the hemorrhages

TABLE 3—Data on Three Groups of Cataract Extraction

	Group 1 *	Group 2 †	Group 3 ‡
Leaky wounds	17%	11%	9%
Hemorrhage in anterior chamber	15%	11%	8%
Intracapsular extractions	75%	81%	83%
Unintentional rupture of capsule	20%	10%	8%
Round pupil	64%	80%	95%
Vitreous presented	2%	1%	1%
Prolapse of iris	2%	1%	1%
Secondary glaucoma	2%	2%	1%
Detached retina	1%	0%	0%

* Group 1 (100 consecutive cataract extractions). A corneoscleral section with conjunctival flap was made with a Graefe knife. Corneoscleral sutures were introduced after the section.

† Group 2 (100 consecutive cataract extractions). A conjunctival flap was first raised. A Stallard type of suture was introduced before the section, which was made with a keratome and enlarged with scissors.

‡ Group 3 (100 consecutive cataract extractions). A conjunctival flap was first raised. A McLean type of suture was introduced and a long beveled section made with the keratome and enlarged with keratome and scissors.

TABLE 4—Visual Results with Three Methods of Cataract Extraction

Visual Acuity	Group 1 (100 Cases)	Group 2 (100 Cases)	Group 3 (100 Cases)
20/15	40	43	49
20/20	17	20	21
20/25	26	19	13
20/30	2	5	3 { 1 High myopia with chorioretinal changes 1 Corneal opacity (old) 1 Acute glaucoma iridectomy 6 yr before cataract 1 Central chorio retinitis (old) 2 High myopia with changes of chorio retinitis 1 Vitreous opacities
20/40	3	2	6 {
20/50	4 { 1 High myopia, chorioretinitis 2 Chorioretinitis (old) 1 Iridocyclitis		
20/70		1 Old corneal opacity	
20/100	1 Chorioretinitis (old)	2 Chorioretinitis (old)	{ 1 Central chorio retinitis (old) 1 Corneal opacities (old), trachoma 1 Corneal dystrophy (old)
20/200 or less	4 { 1 Retinal detachment 1 Diabetic retinopathy 1 Diabetic retinopathy and secondary glaucoma 1 Chorioretinitis (old)	1 Cosmetic ext (blind eye) 1 Iridocyclitis and sec ondary glaucoma	4 { 1 Albino with nystagmus 1 Central retinitis 1 Macular degenera tion (both eyes) 1 Iridocyclitis
		1 Died in hospital	1 Patient died before vision determined
	100	100	100

were small, in some cases being only a slight blood stain of the iris, this is a great improvement over the results of the 100 extractions in group 1

Table 3 summarizes the data for the three groups and shows a definite improvement as the series progressed. In groups 2 and 3 more freedom was allowed the patients during convalescence, this added greatly to their comfort and caused no apparent harm to their eyes.

In table 4 are given the visual results. In each group is included the usual number of complicated cataracts in which there was some preexisting condition that affected the sight. To evaluate properly the three methods of cataract extraction, such complicated cases probably should be omitted.

In the three groups, there was a progressive increase in the percentage of cases in which more acute vision was obtained. In group 1 there were 60 per cent in which vision was 20/20 or better, in group 2, 68 per cent, and in group 3, 70 per cent.

Although 7 cases with high myopia and fluid vitreous are included in groups 2 and 3, there was no case in which vitreous presented during or directly after the section, as is occasionally seen with the Graefe section. Possibly the reason is that the globe is distorted so little with the section made with the keratome and scissors as compared with the section made with the Graefe knife.

It is appreciated that with such a small series definite conclusions cannot be drawn, however, a careful analysis of even a few cases is of value.

CONCLUSION

The long-beveled corneal section with conjunctival flap made with keratome and scissors is safe.

With it the number of postoperative leaky wounds was reduced in the series reported here.

Hyphema still occurred, but the hemorrhages were smaller and less frequent.

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REFRACTION BY THE ASTIGMATIC EYE

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NEW YORK

REGULAR ASTIGMATISM

WHEN the refracting power of the eye as a whole, instead of being identical in all meridians, changes gradually from one meridian to the next by uniform increments, and when each meridian has a uniform type of curve throughout the refracting zone, the condition is known as regular astigmatism. This is the condition that ordinarily is corrected by a cylindric or spherocylindric spectacle lens.

Regular astigmatism usually is caused by a toroidal, instead of a spherical, curvature of one or more refracting surfaces of the eye. Occasionally it results from an oblique or tilted position of the lens with respect to the optic axis. Other causes are rare.

When two or any larger number of cylindric or spherocylindric refracting surfaces are combined with their axes in varying positions with respect to each other, the result always will be a spherocylindric equivalent, in which the meridian of greatest curvature is at right angles to the meridian of least curvature. Consequently, it does not matter if, in one or more of the refracting surfaces of the eye, the meridian of greatest curvature actually is crossed obliquely by the meridian of least curvature, instead of at a right angle. The resultant effect always is that of a spherocylindric combination in which the meridians of greatest and least curvature are arcs of circles at right angles to each other. The intervening meridians will have a correspondingly greater or lesser curvature, but they will be the arcs of ellipses and not the arcs of circles.

PATH OF LIGHT THROUGH AN ASTIGMATIC EYE

A beam of light that enters an eye from a luminous point outside is limited by the circular aperture of the iris. In an emmetropic eye the beam converges symmetrically to form a tiny pointlike image on the retina. Actually, this tiny image is a diffraction pattern, consisting of a relatively bright central disk (about 0.011 mm in diameter) surrounded by several relatively dim concentric rings of rapidly diminishing brightness. For practical purposes, only the central disk need be considered.

In an astigmatic eye the beam of refracted light starts to converge toward a focus but not equally in all meridional planes¹ Only in two planes, the principal planes, is an actual focus reached The first focus is in the plane of the meridian of greatest curvature The second focus is in the plane at right angles, the plane of the meridian of least curvature The interval between the two focal planes is proportional to the amount of astigmatism

The curvature of only the two principal planes is circular, or constant In the intervening meridional planes it is elliptic² No focus is reached in any of the intervening planes The rays which enter through these planes do not remain in the same plane before and after refraction³ They run in directions which are skew to the optic axis and do not intersect the latter

1 A meridional plane is one which passes through the normal to the corneal vertex, the optic axis

2 Unlike the arc of a circle, the arc of an ellipse has a varying curvature It is flattest where it meets the minor axis, and from there the curvature increases equally in both directions, to reach a maximum at the points of intersection with the major axis

In an astigmatic eye the optic axis serves as a common minor axis for the elliptic refracting arcs of the innumerable meridional planes Since, in a given medium, refracting power, or proximity of focus, is directly proportional to curvature, it is understandable that in the meridional planes refracting power increases with the distance along the elliptic arc from the optic axis

3 The course of a plane beam of light, after refraction through the elliptic curve of an oblique meridional section of a spherocylindric refracting element, can be visualized with the aid of a projector and some converging lenses Two strips of adhesive tape should be pasted across one surface of a cylindric lens so as to produce a very narrow slit oblique to the axis of the cylinder Then, in combination with a spherical lens, the cylindric lens is fastened in front of a projector, the taped surface being nearest to the projector A stenopaic slit may be placed next to the cylinder instead of the two strips of adhesive tape, if desired Then a small circular beam of light is sent through the projector, and the light that emerges through the slit is studied by being intercepted at various distances with a small screen

The oblique slit allows only a plane beam of incident light, rectilinear in cross section, to be refracted by the lenses Immediately after refraction, the straight line, which represents the cross section of the narrow beam, starts to rotate along and about the optic axis Simultaneously, the line starts rather rapidly to decrease in length A minimum length, which is only a fraction of the length of the slit, is reached after rotation of about 75 to 90 degrees has occurred Thereafter, the beam widens out again and continues its rotation The rotation ceases after a total angle of from 140 to 170 degrees has been covered Then the beam remains at its final inclination while its width (cross sectional length) increases indefinitely

By placing a very narrow strip of tape transversely across the slit at various places the location of each point in the slit through the refracted beam can be ascertained from the corresponding shadows It will be observed that, as the beam rotates and changes in width, each point in the slit maintains the same

(Footnote continued on next page)

Thus, in an astigmatic eye rays converge to a focus on the optic axis⁴ in only two planes. These two principal planes always are at right angles to each other. A focal line which is perpendicular to the optic axis runs in each principal plane through the focal point of the other plane. The rays that enter in meridional planes other than the two principal planes pass through the two focal lines but do so away from the optic axis, which they do not intersect.

This varying refraction for different planes of incidence causes the initially circular beam of light to undergo characteristic and successive changes of contour. At first the cross section of the refracted beam is bounded by a progressively narrowing ellipse with its major (longer) axis in the plane of the meridian of least curvature and its minor (shorter) axis in the plane of the meridian of greatest curvature. Both axes diminish at uniform rates, the minor axis doing so more rapidly than the major axis. When the minor axis has decreased to a point, the ellipse has narrowed to a line—the first focal line. This line lies in the plane of the meridian of least curvature and is perpendicular to the optic axis. Beyond the first focal line the pointlike minor axis starts to increase and does so at the same rate at which it previously

relative position in the cross sectional line. This indicates that the refracted rays do not intersect the optic axis.

Even though the rays of the oblique sections do not intersect the optic axis, they must pass through the two focal lines. The rotation of the refracted beam must harmonize with the position of the two focal lines. Therefore in order that all rays may pass through the first focal line, the initial direction of rotation in all oblique meridional planes is toward the plane of the meridian of least curvature. After the first focal line has been passed, all rotation continues, so that at the second focal line all rays will lie in the plane of the meridian of greatest curvature. The rotating beams reach their minimum widths at various points along the interval between the two focal lines. The final position of rotation is reached in each plane in the space beyond the second focal line but rather close to it. These positions can be verified by simply removing the tape from the slit and observing the location of the two focal lines.

A crude model of the surface generated by such elliptic refraction of a plane beam of light can be made by pushing a series of toothpicks of proportionate decreasing and increasing lengths through and along the length of a drinking straw. The straw represents the optic axis, and the toothpicks are inserted in directions that correspond with the observed positions of the cross sections of the refracted beam. It is difficult to describe the resulting surface. Roughly, it may be said to resemble a helicoidal surface. Consideration of this surface indicates that the individual rays, in order to maintain rectilinear paths, as demanded by the theory of light, must pursue directions that are skew to the optic axis. The rays all cross the optic axis obliquely, but they are separated from it by varying intervals, and they do not actually intersect it.

4 The optic axis is not identical with the visual axis in the eye. An angle of about 5 degrees separates them at the nodal point. However, this slight separation does not materially impair the conclusions of this theoretic consideration.

decreased. The major axis, meanwhile, continues to shrink. When the two axes become equal in length, a circle is formed—the circle of least confusion. Beyond the circle the former minor axis becomes the major axis for the new series of elliptic cross sections and vice versa. Finally, a second focal line, perpendicular to the first, is formed in the plane of the meridian of greatest curvature. It passes through the focal point of the meridian of least curvature, perpendicular to the optic axis. Beyond the second focal line the beam continues to expand indefinitely in an elliptic contour with major axes in the plane of the meridian of greatest curvature.

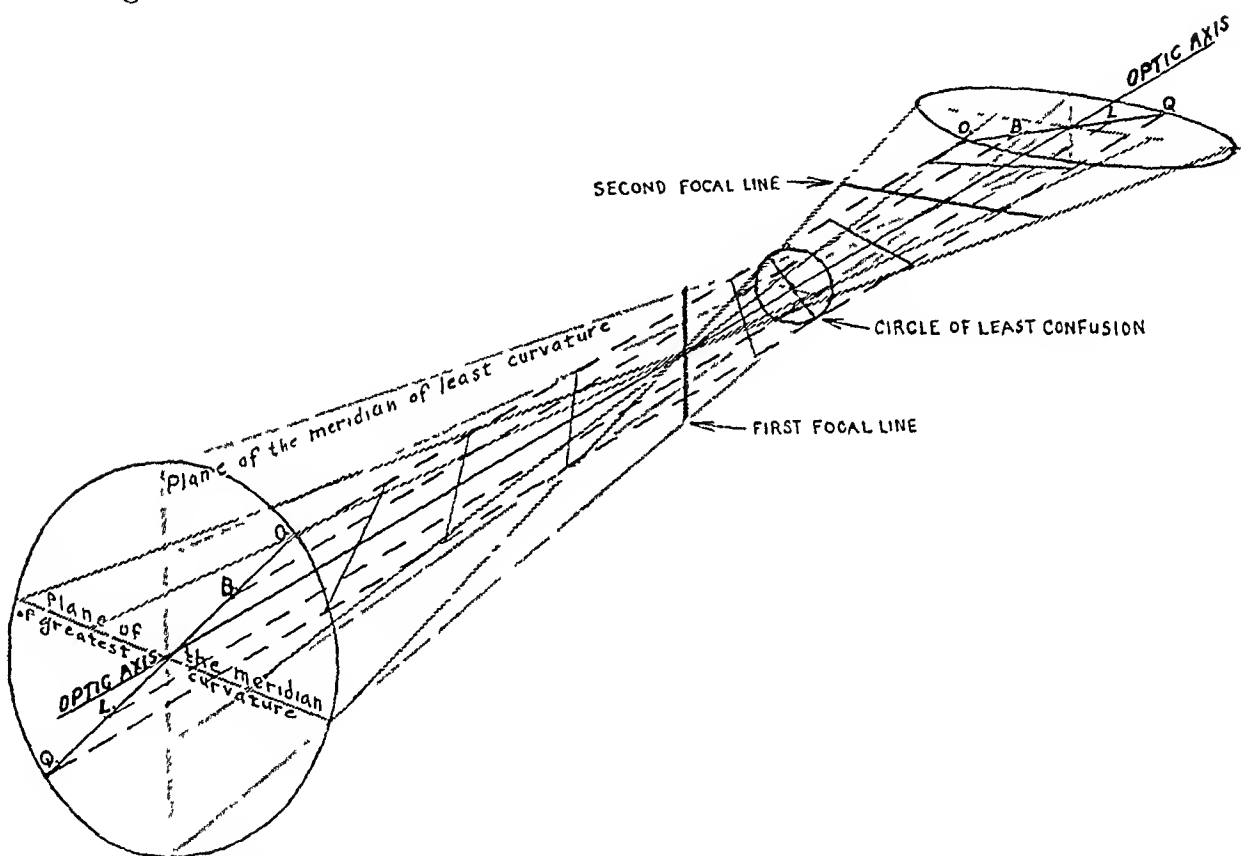


Fig 1—Schematic drawing which attempts to show the course of some of the individual light rays in Sturm's conoid. The course of the rays in an oblique meridional plane of incidence is particularly stressed. The paths of four rays (designated O, B, L and Q) which enter through such a plane are shown. They are depicted with interrupted lines in order to make it easier to follow their courses. Also, they are connected at various intervals by cross sectional lines, which indicate the progressive rotation that the original plane of incidence undergoes after refraction. The focal lines have been darkly shaded in order to indicate that they have a slight width.

The foregoing description of the contours of an astigmatic beam of light makes it evident that the image of an object point never can resemble a point. It must be, depending on the position of the retina, a diffusion pattern corresponding to an ellipse, a circle or a straight line.

The distances of the two focal lines behind the optical elements of an astigmatic eye vary inversely with the dioptric powers of the two

principal refracting meridians The interval between the two lines, the interval of Sturm, depends on the amount of astigmatism—the difference between the dioptric powers of the two principal meridians

THE FOCAL INTERVAL OF STURM

The whole bundle of refracted astigmatic rays is known as Sturm's conoid As already mentioned, the part which lies between the two focal lines is called the focal interval of Sturm Within this interval is the circle of least confusion It is of interest to determine mathematically the location of this circle within the interval This can be done with the aid of figure 2, which is a geometric representation of Sturm's interval The two principal planes have been rotated about the optic axis so as to lie in the same plane The following designations have been made in the figure F_1 for the first focal point, F_2 , for the second focal point, f_1 , for the distance from the posterior principal plane of the eye to the first focal line, f_2 , for the similar distance to the second focal line, a , for the length of the radius of the incident cylindric beam of light, c , for the radius of the circle of least confusion, and z , for the distance from the first focal line to the circle of least confusion

From similar triangles

$$\frac{c}{a} = \frac{z}{f_1}$$

and

$$\frac{c}{a} = \frac{f_2 - f_1 - z}{f_2}$$

Therefore

$$\frac{z}{f_2 - f_1 - z} = \frac{f_1}{f_2} \quad (1)$$

or

$$z = \frac{f_1 (f_2 - f_1)}{f_1 + f_2} \quad (1 A)$$

It is evident from equation (1) that the circle of least confusion divides Sturm's interval into two lengths which are proportional to f_1 and f_2 Since f_2 always is numerically larger than f_1 , the circle of least confusion cannot be midway between the two focal lines but must lie slightly nearer to F_1

Since f_1 and f_2 represent the reciprocals of the posterior refracting powers of the two principal meridians, and since the latter, in turn, are proportional to the anterior refracting powers (the posterior refracting power multiplied by 1.336, the index of refraction of the vitreous, equals the anterior refracting power), f_1 and f_2 may be replaced in equation

(1) by $1/D_1$ and $1/D_2$, the latter symbols representing the anterior refracting powers of the two principal meridians. This changes equation (1) to

$$\frac{z}{f_2 - f_1 - z} = \frac{D_2}{D_1} \quad (1B)$$

According to Gullstrand, the anterior refracting power of the eye varies from 58.64 D, with the accommodation relaxed, to 70.57 D, in maximum accommodation. Ordinarily, astigmatism of more than 4 D is unusual, while astigmatism of more than 6 D is rare. By substituting values in equation (1B) which cover a range of refracting powers from as low as 50 D to as high as 80 D and a range of amounts of astigmatism from 1 to 6 D it can be seen that the ratio $\frac{z}{f_2 - f_1 - z}$ varies from $\frac{1.0}{1.01}$ to $\frac{1.0}{1.1}$. Thus, although the circle of least confusion actually lies closer to the first focal line than to the second, for all practical purposes it may be regarded as lying midway between the two focal lines in the astigmatic eye. Even with 6 D of astigmatism in an eye with minimal refractive power the forward displacement of the circle from the midposition corresponds to hardly more than $\frac{1}{4}$ D of refractive power.

An equation for the size of the circle of least confusion also is easily obtained from figure 2

Since

$$\frac{c}{a} = \frac{z}{f_1}$$

and

$$z = \frac{f_1 (f_2 - f_1)}{f_1 + f_2}$$

$$\frac{c}{a} = \frac{f_2 - f_1}{f_1 + f_2}$$

or

$$c = \frac{a (f_2 - f_1)}{f_1 + f_2} \quad (2)$$

• It is apparent from equation (2) that the size of the circle of least confusion is proportional to the size of the radius of the incident beam of light or, what amounts to the same thing, to the diameter of the pupil of the eye. When the pupil is small, the circle is small. Also, the smaller the amount of astigmatism, the smaller will be the circle of least confusion.

PRACTICAL APPLICATIONS

The desideratum in the correction of astigmatism is a twofold one—the elimination of the interval of Sturm by making the two focal points of the principal meridians coincide and the displacement of the

resultant nonastigmatic image on the retina. However, many persons with astigmatism will not tolerate an immediate full correction. The resulting unequal prismatic distortions and displacements of objects are too annoying. In cases of this kind the oculist should strive to

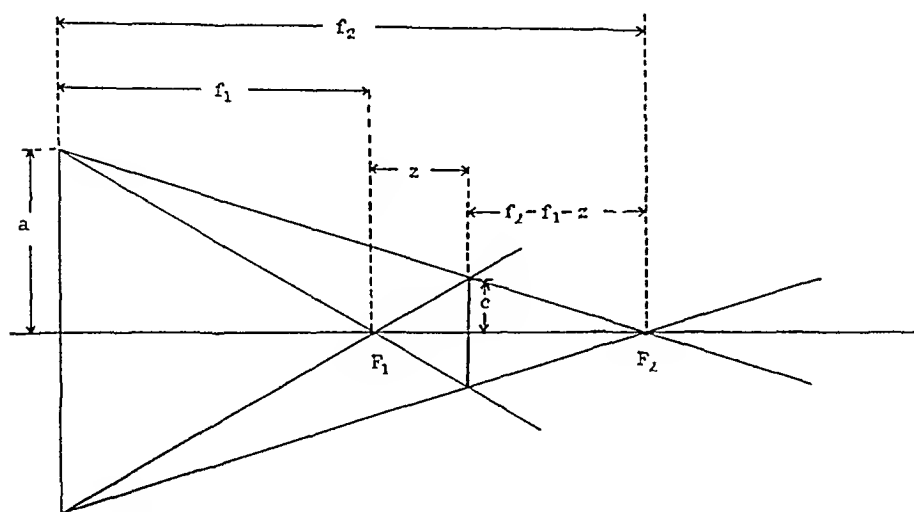


Fig 2—A geometric representation of Sturm's conoid

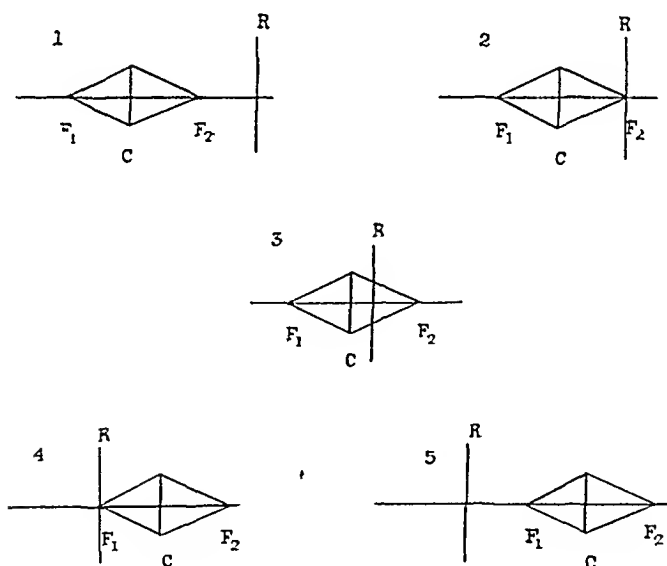


Fig 3—Diagram illustrating the position of the focal lines (F_1 and F_2) and the circle of least confusion (C) with respect to the retina in the various astigmatic conditions. 1 shows the positions in compound myopic astigmatism, 2, in simple myopic astigmatism, 3, in mixed astigmatism, 4, in simple hypermetropic astigmatism, and 5, in compound hypermetropic astigmatism.

do two things. First, he should reduce the interval of Sturm, and with it the size of the circle of least confusion, by a partial correction of the cylindric error. Then, with spherical correction he should shift the position of the reduced astigmatic interval so as to bring the

circle of least confusion on the retina. In the absence of a full correction it is believed that an astigmatic eye will have its clearest and most comfortable vision whenever the circle of least confusion coincides with the retina.

The position of the two focal lines relative to the position of the retina is revealed by refraction. These lines can be shifted by means of spectacle lenses. A converging lens moves images forward, and a diverging lens displaces them backward. Spheres affect all meridians equally and will shift F_1 and F_2 through equal intervals. Cylinders exert a maximum effect in the meridian at right angles to the axis and have no effect in the meridian parallel to the axis. Correctly placed, a cylinder will shift the position of only one of the two focal lines—the one that is farther from the retina—and will not change the location of the other.

In those cases in which only a partial correction of the astigmatism seems advisable there must be added to the partial cylindric correction a spherical correction sufficient to move the circle of least confusion on to the retina. The amount of spherical power that is required is half the dioptric value of the remaining uncorrected astigmatism (the circle of least confusion is approximately in the middle of the focal interval) plus the dioptric value of the distance between the retina and the nearer focal line (the second focal line in the myopic eye and the first focal line in the hypermetropic eye). In cases of hypermetropia the spherical power thus calculated must be decreased by an allowance for the accommodative tonus. Two examples will illustrate this rule. If the full correction is -3.00 D sph $\subset -5.00$ D cyl and it is desired to correct only half the astigmatism, the prescription should read -4.25 D sph $\subset -2.50$ D cyl. In the second case, if the total correction is $+6.00$ D sph $\subset +4.00$ D cyl and it is deemed advisable to correct only 2.50 D of the astigmatism, the prescription should read $+6.75$ D sph $\subset +2.50$ D cyl less whatever spherical allowance is made for the strength of the ciliary muscle.

A similar procedure was recommended by Copeland,⁵ who arrived at his conclusions by an obscure graphic method. Copeland stated

if the cylinder is reduced a change must be made in the spherical element of the lens. In reducing the cylindric element of any correction add half of the amount of the reduction to the sphere, maintaining the sign of the cylinder in the addition.

Copeland also introduced the term "spherical equivalent of the compound" for the spherical combination of half the dioptric value of the astigmatic correction plus the spherical correction.

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⁵ Copeland, J. An Official Study in the Application of Cylindric Corrections, *Optom Weekly* 19:191 (April 5) 1928.

SIGNIFICANCE OF ANISEIKONIA IN AVIATION

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THE word "aniseikonia" is derived from the Greek roots *ἀνισος* and *εἰκὼν* meaning literally "unequal image." It may be defined as that condition of the binocular visual apparatus in which the ocular images as seen by the two eyes are unequal in either size or shape or in both. The term ocular image does not refer to the retinal image, but it is applied to the final impression which reaches consciousness in the higher brain centers.

Aniseikonia is of two principal types: (1) over-all difference, in which one image is larger than the other in all meridians, and (2) meridional difference, in which one image is larger than the other in one meridian. Combinations of the two forms may occur. If the ocular images are markedly unequal in size and shape, there may be a disturbance of binocular vision, which may or may not be apparent to the patient.

ANISEIKONIA AND FLYING PERFORMANCE

The significance of aniseikonia in flying performance has been a matter for conjecture since 1935, when Ames¹ first called attention to this aspect of the subject. He aroused interest concerning the importance of aniseikonia in the perception of depth among investigators in the field of aviation medicine. In addition, Ames and his associates showed that aniseikonia affects stereoscopic vision, and he suggested therefore, that the anomalous spatial localization resulting might interfere with the pilot's judgment of distance. Since that time the literature on aviation medicine has contained frequent reference to the possible correlation of flying performance and the presence of aniseikonia. Noteworthy among those who have discussed this subject is Armstrong,² who in his textbook states "that aniseikonia affects stereoscopic vision

Read at a meeting of the Canadian Ophthalmological Society, Montreal, Canada, Sept 21, 1942.

This paper is a resume, with added references, of a report submitted to the Associate Committee on Aviation Medical Research, National Research Council of Canada, July 12, 1942.

1 Ames, A., Jr. Aniseikonia—A Factor in the Functioning of Vision, *Am J Ophth* **18** 1014, 1935.

2 Armstrong, H. G. Principles and Practice of Aviation Medicine, Baltimore, Williams & Wilkins Company, 1943.

and may interfere with the pilot's judgment of distance and may make it impossible for him to correctly estimate the true position of the plane of the earth below him "

It was considered important in the Royal Canadian Air Force to evaluate the significance of aniseikonia in its practical relationship to flying, for three reasons (1) aniseikonia may interfere with stereoscopic vision, as just stated, (2) the presence or absence of aniseikonia is not determined by the routine ophthalmic examination, and (3) there were numerous pilot trainees who had ceased training because of inability to land an aircraft successfully

SELECTION OF CANDIDATES FOR EXAMINATION FOR ANISEIKONIA

The study of the relationship of aniseikonia to flying performance was limited to its correlation with the ability of the airman to land an aircraft successfully To this end, a selected group of 175 pilots who had ceased training was examined for the presence and amount of aniseikonia Also, a control group of 50 experienced pilots, all of whom were instructors, was studied

The 175 airmen were trainees who had ceased training because of one or more experiences with difficulties in landing most important among which was incorrect judgment of height and distance in landing the plane The majority of the airmen examined for aniseikonia had ceased training during the period between the tenth and the fifteenth hour of their flying training In the case of a minority the poor landings were manifested with the faster and heavier aircraft after approximately one hundred flying hours, at which time they were forced to cease training

A suitable form outlining the most important landing errors was utilized at the flying schools in the cases of the airmen who had ceased training because of landing difficulties The form was completed by the medical officer at the flying school, with the assistance of the airman's instructor In addition to landing errors, which were directly attributable to faulty judgment of height and distance, other factors, such as air speed, coordination and nervousness, were included in the table All types of landing errors were noted even though one or more of the errors might occur during a landing as a result of defective judgment of height and distance In this way it was possible to correlate the landing difficulties of the airmen with the data on aniseikonia, obtained later

A control group of 50 experienced pilots was examined for whom the judgment of height and distance was considered to be satisfactory by virtue of their satisfactory landing performance The amount of aniseikonia was determined for each of the experienced pilots

ROUTINE EXAMINATION OF THE EYES

In each case, before the examination for aniseikonia was performed, it was necessary to have general information concerning the condition of the eyes of the airmen or pilot A suitable form was used for the study, which included the data obtained in the routine ophthalmic examination and in the examination for aniseikonia The routine ophthalmic examination was similar to that employed in the categorization of aircrews in the Royal Canadian Air Force This included the assessment of the visual acuity at 20 feet (6 meters) using the Project-O-

Chart and determination of whether or not the manifest hypermetropia exceeded 2.50. The extraocular muscle-balance at 6 meters and at 25 cm was determined by means of the Maddox rod and cover tests. The accommodation in each eye and the objective convergence were ascertained. When indicated, a manifest or cycloplegic refraction was performed.

APPARATUS USED IN MEASUREMENT OF ANISEIKONIA

The examination for aniseikonia was performed with the space eikonometer developed by the Dartmouth Eye Institute. The space eikonometer measures aniseikonia at any axis, in addition to axis 90 and axis 180, and hence it gives direct information as to the nature of a subject's spatial localization. The "leaf room" was also used in additional corroboration of the measurements with the space eikonometer.

CORRELATION OF ANISEIKONIA AND PERFORMANCE FOR 175 PILOTS WHO HAD CEASED TRAINING AND FOR 50 EXPERIENCED PILOTS

In order to interpret the data obtained from the examination for aniseikonia of the 175 pilots who had ceased training and the 50 experienced pilots, it was necessary to correlate the flying performance with these results. The flying performances in landing were conveniently divided into four types. The pilots who had ceased training consistently leveled off too high or too low, or were erratic in landing and leveled off too high or too low at different times. These three types were compared with the performance of experienced pilots whose landing performance was known to be satisfactory. Of the 175 pilots who had ceased training, 48 per cent were found to have leveling off too high as their most important landing fault, 32.6 per cent consistently flew into the ground, and 19.4 per cent were erratic and committed each of these landing faults at different times.

The amount of aniseikonia in the vertical meridian was less than 0.40 per cent in 76.6 per cent of the 175 pilots who had ceased training and in 82 per cent of the 50 experienced pilots (fig. 1A). In the remaining pilots with slightly greater amounts of aniseikonia in the vertical meridian, with which anomalous spatial localization might be expected to be rather pronounced, this degree of aniseikonia was not of practical significance in the landing of aircraft because of the importance of monocular visual clues.³ No significant correlation with performance in landing was found to exist.

3 As a corollary of this study, it was noted that monocular visual clues assume an importance in the judgment of distance in landing aircraft which has not hitherto been sufficiently recognized. In the past it had been considered that this judgment was made by stereoscopic visual clues (a binocular function), and, while such monocular clues as perspective, shadow, overlap and size of retinal image

The aniseikonia in the horizontal meridian was less than 0.40 per cent in 86.4 per cent of the pilots who had ceased training and in 98 per cent of the experienced pilots (fig 1 *B*). No significant correlation with landing performance was demonstrated.

These figures for aniseikonia are in remarkable agreement with the results of Peckham⁴ in a study of 252 aviation cadets and instructors of the United States Navy. He found that 92 per cent of the subjects showed less than 0.50 per cent of aniseikonia.

The determinations of cyclophoria were important in that plus cyclophoria results in binocular visual clues appearing nearer and minus cyclophoria results in binocular visual clues appearing farther away.

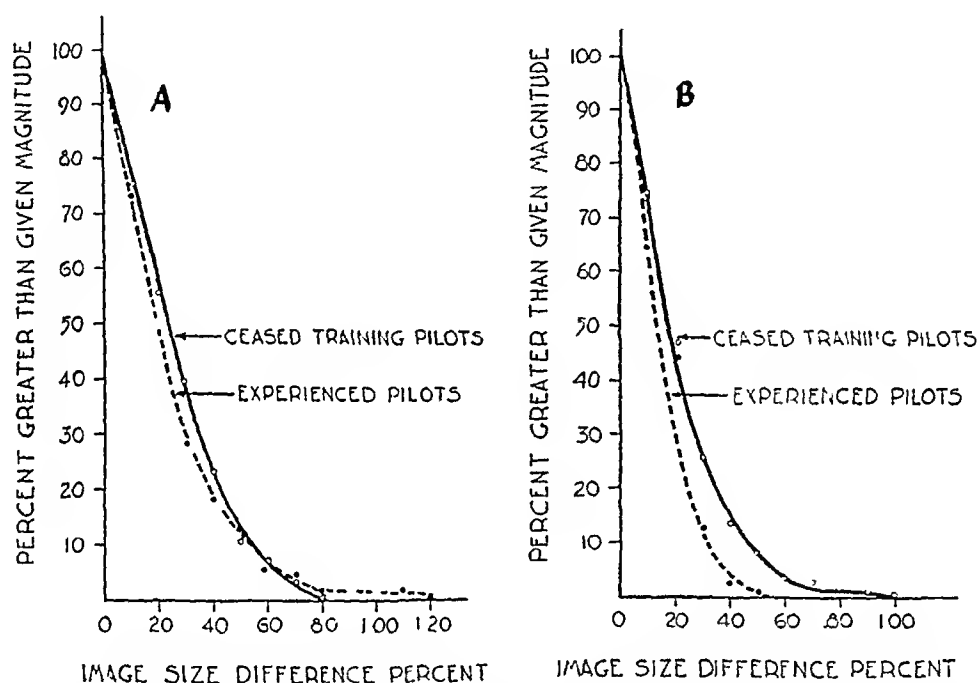


Fig 1—Aniseikonia (*A*) in the vertical meridian and (*B*) in the horizontal meridian in 175 pilots who had ceased training and in 50 experienced pilots.

The conclusion was reached that the values for cyclophoria proved to represent the normal distribution for a highly selected group of the population and that no practical relationship existed between landing performance and the presence of cyclophoria in the groups studied.

were recognized, they were not considered important in the total judgment which the pilot makes in the landing of the aircraft.

Since aniseikonia is a binocular dysfunction, the anomalous spatial clues must be significantly great to overshadow the important monocular clues. In the vast majority of situations in aviation, monocular clues predominate in landing fields both by day and by night, and only in the unusual case do stereoscopic visual clues overshadow the monocular clues.

4 Peckham, R. H., in discussion on Lancaster, W. B. Nature, Scope and Significance of Aniseikonia, Arch Ophth 28:767 (Nov.) 1942.

(fig 2) Peckham⁴ studied the space perception in his subjects by means of their response with aniseikonia lenses to a frontal plane set before them. He felt that there was a significant difference between the two groups on this apparatus.

No significant correlation was noted between landing performance and the standard deviation of the settings on the space eikonometer.

It was shown that no relationship existed between landing performance and the presence of base-out asymmetry lenses or base-in asymmetry lenses.

EFFECT OF ANISEIKONIA LENSES ON ABILITY TO LAND AIRCRAFT

A series of landings were made in aircraft in order to study the practical effect of various aniseikonia lenses on the judgment of height

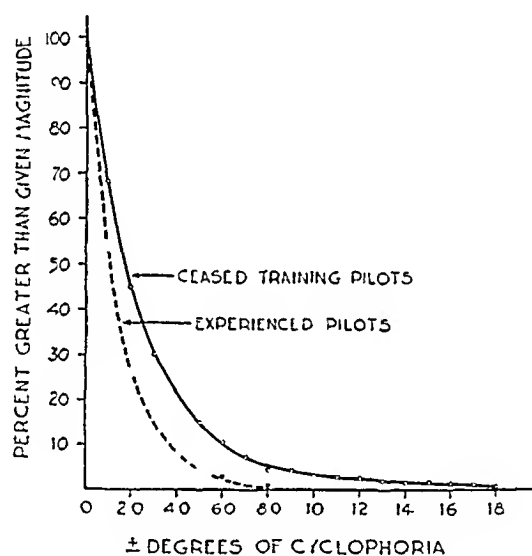


Fig 2—Cyclophoric aniseikonia in 175 pilots who had ceased training and in 50 experienced pilots

and distance. The landings were made in a twin engine service trainer airplane. In this aircraft the pilot and co-pilot were seated side by side and I was immediately behind the pilots. An excellent view in all directions was available both to the pilot and to me, so that I had as good a view of the landing field as the pilot.

A wide selection of aniseikonia lenses was used for this aspect of the study. They included 1, 2 and 4 per cent aniseikonia lenses at axes 45, 90, 135 and 180, in various combinations. The lenses were worn in the aircraft by the co-pilot and by me during the take-off, flight and landing.

The most pronounced effects on the judgment of height and distance produced by wearing aniseikonia lenses were present while we were

landing on a level grass field at some distance from its boundaries, and where no parked aircraft were present. In this situation binocular visual clues are almost the only ones present, and the anomalous spatial localization has a marked effect. When the co-pilot was attempting a landing on this field and was wearing a 1 per cent aniseikonia lens at axis 45 in front of the right eye and at axis 135 in front of the left eye, there was a tendency for him to level off the aircraft too soon, at about 30 or 40 feet (9 or 12 meters) above the ground. When the co-pilot was wearing a 1 per cent aniseikonia lens at axis 135 before the right eye and at axis 45 before the left eye the ground appeared farther away than it actually was, and he had a tendency to fly into the ground. A 1 per cent aniseikonia lens at axis 45 before the right eye and another at axis 135 before the left eye is equivalent to a measurement of $+15$ on the space eikonometer. A 1 per cent aniseikonia lens at axis 135 before the right eye and another at axis 45 before the left eye is equivalent to a measurement of -15 on the space eikonometer. In this study there were only 2 pilots who had ceased training for whom readings of ± 15 were obtained on the space eikonometer. Less marked changes in the apparent distance above the ground occurred when the pilot landed while wearing the various other aniseikonia lenses.

When the co-pilot landed the aircraft on an improved paved runway while wearing 1 per cent aniseikonia lenses at axis 45 in front of the right eye and at axis 135 in front of the left eye, or the reverse, the errors in the judgment of height were almost nil. This airdrome was of the standard type, with many crossed runways, hangars and nearby parked aircraft. Here the important monocular visual clues overshadow the anomalous spatial clues produced by wearing aniseikonia lenses. The judgment of distance in this situation is based largely on the monocular visual clues. In this situation the co-pilot made successful landings while wearing the aniseikonia lenses mentioned.

Neither the co-pilot nor I made any remarkable observations during takeoffs or in flight while wearing the various aniseikonia lenses.

It can be concluded that in the landing of aircraft the presence of 1 per cent aniseikonia lenses at axis 45 and at axis 135 in front of the eyes in either combination has a definite effect on the judgment of distance when predominantly binocular visual clues are present. However, the same lenses have little effect on the judgment of height when monocular visual clues predominate.

CONCLUSION

The relationship of aniseikonia to flying performance in landing of aircraft was investigated in two selected groups. In the first group

there were 175 trainees who had ceased training because of difficulties in landing and in the second group there were 50 experienced pilots

The amounts of aniseikonia were found to be very small, and no practical correlation with landing performance could be ascertained in the groups studied

A series of landings were made in aircraft in order to study the practical effect of various aniseikonic lenses on flying performance during landing. It was noted that when monocular visual clues predominated, as was usually the case, the flying performance was not affected by the anomalous binocular clues produced by wearing aniseikonic lenses

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MEDICAL TREATMENT OF ACUTE GLAUCOMA

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It is certainly a curious, but explicable, fact that by living constantly in the presence of a difficulty man becomes less apt to overcome it—*Prof Dr Charles Nicolle*¹

SELDOM do oculists encounter in the exercise of their profession a more dramatic scene than that of an acute attack of glaucoma

Within a few minutes, sometimes quite suddenly, the patient is stricken with violent pain in one eye, pain which radiates toward the ear, teeth and all over the head and may reach an intolerable pitch. He loses sleep and appetite and frequently is subject to nausea, or even vomiting, and fever. Sometimes, owing to the intensity of the pain, he loses consciousness. At the same time the visual power fails rapidly and in some cases disappears completely in a few hours. In other cases the patient perceives lights as though through fog and surrounded by rainbow-colored rings.

On examining the patient, one finds edema of the lids, there is a constant flow of tears, the conjunctiva is edematous, or even chemotic, and of a dark dusky red color, the cornea is turbid, like unpolished glass, the anterior chamber is shallower than normal, the iris is discolored and narrowed and almost in actual contact with the cornea, the pupil, dilated, oval and eccentrically situated, has taken a grayish green color. On touching the eye, one finds it hard as a marble and terribly painful.

In the presence of this acute attack of glaucoma, knowing that the only remedy available is that of operation, and in spite of the gravity of the symptoms, one has to wait until the eye is brought to such a condition that it can be operated on. Meanwhile, miotics and analgesics are applied. But the patient continues to complain of horrible pain, impossible to bear, which is not relieved by any known analgesic, not even morphine, and the visual power gradually diminishes.

This condition may last for several days—the dreadful pain, driving the patient to the brink of madness, and the hardening of the eye to the point of blindness—until, at long last, the oculist can operate—always under extremely difficult conditions and always running the great risk of hemorrhage by thorough sudden decompression. And often the operation has been too late to save the eye.

¹ Cited by *Un Asclepiode, Clinica, Barcelona* **12** 127, 1935

All of us oculists have seen and suffered in the face of such cases, which always leave with us a bitter taste of our own impotence

TECHNIC OF RETROBULBAR ANESTHESIA

In 1914 Pooley² extended to all ophthalmic surgery the anesthetic maneuver used before only for enucleations and eviscerations, by Siegrist³ (1907) and by Elschmig⁴ and Lowenstein⁵ (1908), thus completing the anesthetic technic for operations on the eye. This measure consisted in injecting the anesthetic solution into the apex of the orbit, infiltrating the retrobulbar tissues and, by blocking all the sensory nerves of the eye—the long ciliary nerves, efferent branches of the ciliary ganglion, and the short ciliary nerves, branches of the nasal nerve—obtaining their functional section. This maneuver rendered painless each step of all ophthalmic operations and was immediately accepted the world over. It can be said of every oculist that to know the method was to adopt it immediately. Since then, the retrobulbar injection of an anesthetic has become a necessary preliminary step to almost every operation on the eye.

Among ourselves, ophthalmologists in Mexico, I cannot state who was the first to use it, or when, but I have enough information to be able to state that in 1918 it was in everyday use in the Hospital de Nuestra Señora de la Luz, which was the first institution in Mexico to adopt this form of anesthesia. (In his thesis Palacios Macedo,⁶ refers to the technic used in this hospital, which I myself described to him at the time he was writing the thesis, in 1918.) The anesthetic solution in use now, and for many years, in the Hospital de Nuestra Señora de la Luz is as follows:

Distilled, boiled water	100 cc
Procaine hydrochloride	2.00 Gm
Sodium chloride	0.50 Gm

(in sterilized vials)

If necessary, 0.1 cc of a 1:1,000 solution of epinephrine hydrochloride is added to each cubic centimeter immediately before using. This quantity (1 cc) is the amount used for the retrobulbar injection of the anesthetic.

2 Pooley, G. H. Improvement in Local Anaesthesia in Operations upon the Eyes, *Ophthalmoscope* **12** 464-467, 1914.

3 Siegrist, A. Lokalanästhesie bei Exenteratio und Enucleatio bulbi, *Klin Monatsbl f Augenh* **45** 106-109, 1907.

4 Elschmig, A. Hilfsverfahren bei der Altersstarektaktion, *Arch f Augenh* **98** 300-305, 1927.

5 Lowenstein, A. Ueber regionale Anasthesie in der Orbita, *Klin Monatsbl f Augenh* **46** 592-601, 1908.

6 Palacios Macedo, J. Local and Regional Anaesthesia in Head and Face Operations, Thesis, Mexico City, Universidad Nacional de Mexico, 1919.

In using this injection, my colleagues and I were all able to observe the following results: complete anesthesia of the ocular globe and its annexa, rapid and complete dilation of the pupil and noticeable lessening of the intraocular tension. Sometimes, indeed, the eye becomes softer than desired, for many operations, such as the incision for cataract operation, are made more difficult by too great a softening of the eye. On occasions this softening may even cause complete corneal collapse. Day by day we saw all this and were most familiar with all these effects. But none of us associated the action of the drug with the relief of acute glaucoma.

APPLICATION TO TREATMENT OF ACUTE GLAUCOMA

Once, when I was confronted with a difficult operation on an exceedingly softened eye, I found myself thinking: "If this injection removes the pain and softens the eye to such a degree, it must be the rational treatment for an acute attack of glaucoma."

Afterward, in my mind the thought persisted: "The constant pupillary dilatation adds to the obstruction of the iridocorneal angle, the straining angle, and may thus be harmful to the eye in a case of glaucoma." "Why is the pupil dilated, and why, at the same time, is the ocular tension lessened?"

The German Bayer's Novocain and the American Abbott's procaine, in themselves chemically identical (β -diethylaminoethyl-*p*-aminobenzoate hydrochloride), are synthetic cocaine substitutes, much less toxic than cocaine and with no action on the sympathetic nerve to the iris. These agents are not likely to cause pupillary dilation or softening of the eye.

Epinephrine is, of course, a stimulant of the sympathetic nerve. But the quantity (0.0001 Gm.) which we inject in a cubic centimeter of our anesthetic solution and the place where it is injected minimize its direct action on the dilatory muscles of the pupil. On the other hand, the amount is sufficient to produce a strong constriction of the ciliary vessels, by contact, on infiltration of the retrobulbar tissues. This action of epinephrine on the eyes, fully described by Darier,⁷ according to the experiences of Zimmermann, Wessely, Lewandowsky, Darier and others, is exerted directly on the walls of the vessels, and the anemia which results from the constriction of the vessels of the iris and ciliary body always causes the lessening of ocular tension and produces the dilatation of the pupil by diminishing the volume of the iris and the ciliary body. Grandclément,⁸ of Lyons, affirmed that instillation of epinephrine might be a

7 Darier, A. *Leçons de thérapeutique oculaire faites à la Faculté de Médecine de Paris*, Paris, Bureau de la clinique ophtalmologique, 1901, pp. 120-128.

8 Grandclément, cited by Darier, A. *Traité complet de thérapeutique oculaire*, ed. 2, Paris, Jouve et Cie, 1923, p. 283.

good treatment for inflammatory glaucoma. It has been usual (as recommended by all the great oculists) to add epinephrine to miotic collyria, the action of which it tends to increase.

Thinking over all this, I became convinced that I had found, theoretically, the ideal treatment for an acute attack of glaucoma.

To prevent pupillary dilation and to lengthen the effects of the retrobulbar injection, I instilled before and after the injection, taking advantage of the anemia of the eye, a 1 per cent solution of pilocarpine nitrate and a 0.5 per cent solution of physostigmine salicylate, from the very first time I tried to realize my idea, and I was gratified with magnificent results.

In November 1941 I presented a report of my efforts before the Ophthalmological Society of the Hospital de Nuestra Señora de la Luz, and this study was published in the hospital's bulletin of the same month.⁹ The results of my first experiences could not have been more encouraging.

This procedure has been since then, in constant practice in this hospital in every case of acute glaucoma. More than 200 patients have been successfully treated with the retrobulbar injection of 1 cc of a 2 per cent solution of procaine hydrochloride with the addition of epinephrine hydrochloride (0.0001 Gm per cubic centimeter), always preceded and followed by instillations of pilocarpine and physostigmine. In our hospital, this method has become a matter of routine, and invariably produces the same results. In a few minutes (in 1 case in only six minutes) the pain disappears completely, and we also note the rapid and complete disappearance of all signs of ocular hypertension, that is, the opacity of the cornea, caused by edema, clears, the pupil contracts strongly under the effect of the miotics, the conjunctiva acquires a pale (normal) color, the eye softens and, when this is still possible, the visual power improves and the field of vision is enlarged. These eyes have been operated on, days or weeks later, under perfect conditions of tension for the operation, and without the patient having suffered a recurrence of the pain.

The following year, in 1942, Levitt¹⁰ published an article on the practical treatment of glaucoma, in which he referred to the retrobulbar injection of procaine, alone or with mechlorolchloride, as a means of relieving ocular tension and so of obtaining better conditions under which to operate. In the resume of his work that I have read, it is not specified whether he uses the injection as a preoperative step only. I do not know, therefore, whether he and I are in agreement.

9 Icaza, M. J. Un paliativo útil en el glaucoma agudo, *Bol. d. Hosp. oftal. dc Ntra. Sra. de la Luz* 1: 258-260, 1941.

10 Levitt, J. M. Practical Management of Primary Glaucoma, *Dis. Eye, Ear, Nose & Throat* 2: 249-251, 1942.

as to its use, aside from the operative technic. In any case, Levitt's article was written and published in August 1942 nine months after mine, of November 1941.

COMMENT

Of course I do not believe that this treatment is the remedy for glaucoma. But I am convinced that it is the most useful palliative measure yet found, with which one is able first to give the patient complete relief from great pain and, second, to put the eye in such condition as to permit the surgeon to choose without haste the treatment which he may judge most adequate in each case and to apply it at exactly the right time, without danger of complications.

I do not pretend to be the initiator of the retrobulbar injection, which has been known and used for a long time. But it had been always employed only as a preliminary step to the operation, as a part of the anesthetic technic. To the best of my knowledge, I was the first to use it as a method of treatment in itself, applied at the very moment of an acute attack of glaucoma.

Considering that it may prove of practical utility I have decided to publish my experiences with this treatment, in the hope that oculists who may do me the favor of reading about them may find a simple and harmless method, available at any moment, which they may use repeatedly if necessary (I have not yet needed to repeat the injection) to fulfil the two most urgent needs in an acute attack of glaucoma, namely, the deadening of the pain and the lessening of the ocular tension, alleviating in this way the patient's unbearable pain and at the same time conditioning the eye to receive definite surgical treatment.

CATARACT ASSOCIATED WITH INTRAOCULAR TUMORS

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IN FOUR previous papers, I¹ described the microscopic observations in cataracts associated with ulcers of the cornea,^{1a} scars of the cornea,^{1b} spontaneous iritis^{1c} and detachment of the retina^{1d} and traced the causes of these cataracts. The present paper, the fifth of the series, concerns cataracts which develop in the course of intraocular tumors.

Fortunately, in most cases the lens is not affected by the tumor in the preglaucomatous stage, and the examination of the fundus is unhindered. However, it may happen in the early stages of a tumor that a mistaken diagnosis of incipient cataract is made because the changes in the lens would seem to be enough to explain the visual disturbance. In the glaucomatous stage a combination of cataract, iridocyclitis and glaucoma may present a picture so complicated that a tumor would not be suspected as the underlying cause.

In the routine of clinics, a special cause of diagnostic error in a case of a tumor concealed by a cataract is failure to obtain a complete history. In response to ordinary questioning a patient is apt to give symptoms similar to those elicited in a case of detachment of the retina, because a tumor of the choroid may cause but slight visual disturbance prior to the detachment of the retina. It is only by putting direct questions to a patient that he can be made to recall that the earliest sign of disturbance of vision was a distortion of objects, or an impression of dark waves before the eye, or a sensitiveness to light in a certain quadrant, or dizziness. Often it is not until the globe is inflamed and painful that the patient consults the oculist.

MATERIAL

The material for the present paper consisted of microscopic preparations from 57 globes, each containing an intraocular tumor. In 34 globes the tumor was a malignant melanoma and in 21 globes a retinoblastoma. In 1 globe there was an

Read at the Eighty-First Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., Nov. 11, 1945.

1 Samuels, B. (a) Lesions in the Lens Caused by Purulent Corneal Ulcers, *Tr. Am. Ophth. Soc.* **39** 66-72, 1941, (b) Cataract Complicating Corneal Scars After Perforating Ulcers, *ibid.* **40** 292-304, 1942, (c) Pathology of the Lens in Non-Traumatic Iritis, *ibid.* **41** 262-272, 1943, (d) Complicated Cataract Associated with Spontaneous Detachment of the Retina, *ibid.* **42** 109-117, 1944.

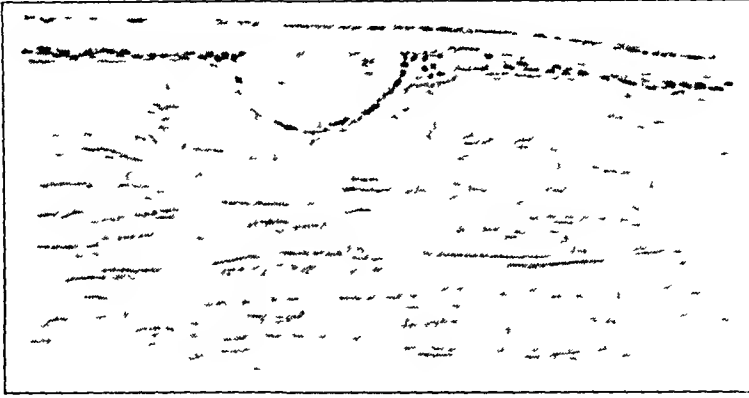


Fig 1—Detachment of subcapsular epithelium by a druse in a case of malignant melanoma of the choroid in the globe of a girl aged 17 years. The drawing is of a section from the pupillary area. The subcapsular epithelium is detached by a hemispherical mass resembling the capsule of the lens in staining reaction, although it lacks its uniform quality. At its base the epithelium exhibits some proliferation. A few fibroblasts are scattered over the anterior surface of the capsule.

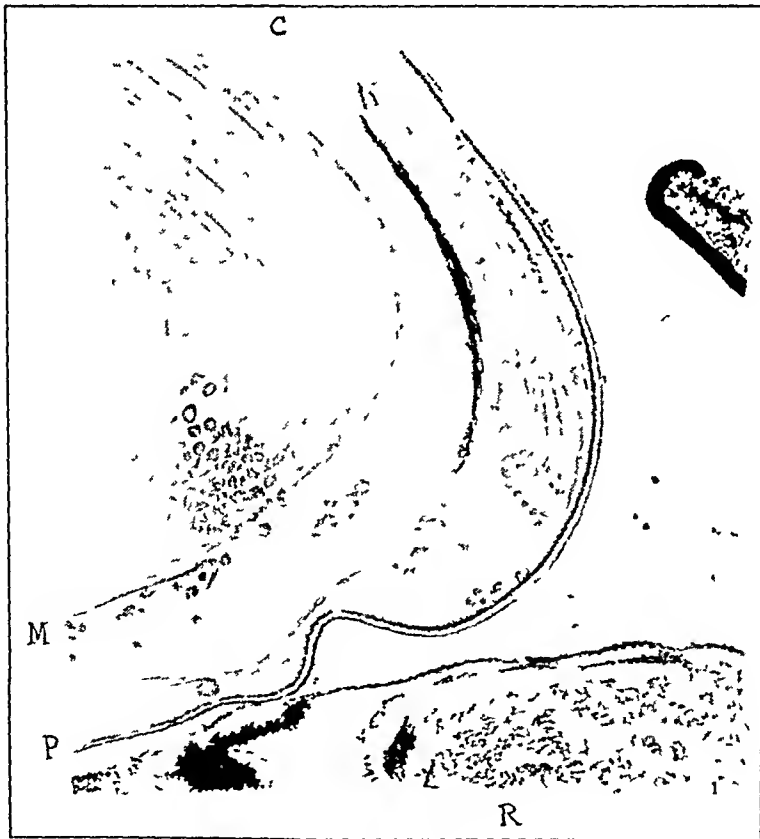


Fig 2—Morgagnian globules and calcification in a case of retinoblastoma. The nucleus of the lens is more darkly stained than the cortex (C). Capping the equator is a thin crust of chalk. Posteriorly, at P, the lenticular cells are disintegrating. A number of Morgagnian globules (M) are present in the cortex, and a group of them are in the nucleus. The degenerated retina (R) is in contact with the lens.

epithelioma of the ciliary body and in another a sarcoma that invaded the ciliary body from the limbus. Considering how long a lens may remain unaffected in a case of intraocular tumor, the material is indeed a large one.

In the course of this paper it will be brought out that the tumor was not in every instance the actual sole cause of the cataract. Complications that developed in the globe during the growth of the tumor or during its degenerative change were either the direct or the contributing factor in formation of some of the cataracts. It suffices to say here that of the 57 tumors 26 were in contact with the lens. Seventeen of the melanomas were necrotic, 12 were almost entirely so, and all the retinoblastomas showed signs of necrosis.

PATHOLOGIC DETAILS

1 *Folds in the Capsule*—In a discussion of anatomic details, folds of the capsule deserve to come first, because they are among the most conspicuous of all the changes to which the lens is ordinarily subjected.

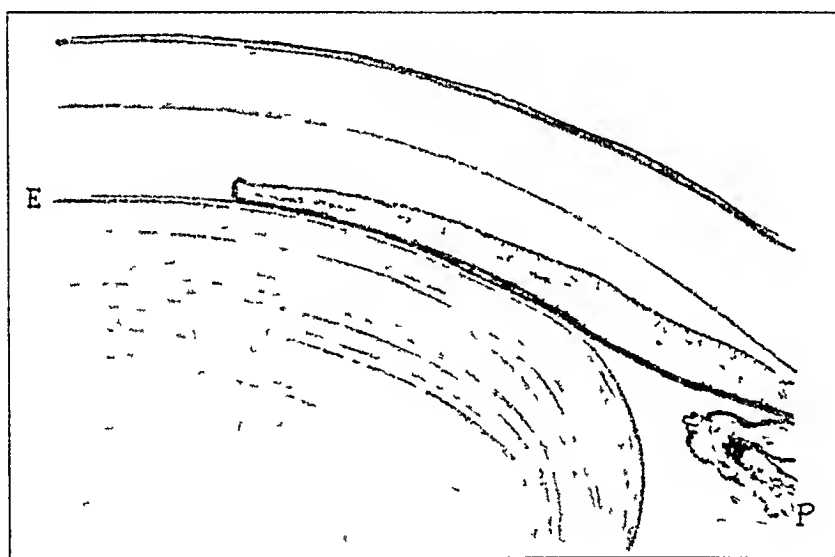


Fig. 3—Necrosis of epithelium under a necrotic pupillary zone in a case of malignant melanoma of the choroid in a globe of a woman aged 40 years. The lens was pressed forward by the detached retina. The epithelium of the lens (E) is normal in the pupillary opening and at the equator. Between these two areas, exactly where the necrotic iris comes in contact with the lens, there is a stretch in which the epithelium has disappeared. The sphincter muscle is gone, as are the chromatophores in the stroma to a great extent. The ciliary processes are necrotic, and their pigment layer is dispersed. The anterior chamber is shallow, and the filtration angle is blocked.

However, in this survey, folds were lacking in a majority of the cases. In the cases of retinoblastoma folds were found but once, and then in connection with a large anterior polar cataract that threw the overlying capsule into numerous ruffles. The tumor was surprisingly small and showed but little necrosis. The iris was greatly inflamed. Iritis is rarely present in cases of retinoblastoma, although early necrosis is a characteristic of this tumor. In this case it was not believed that

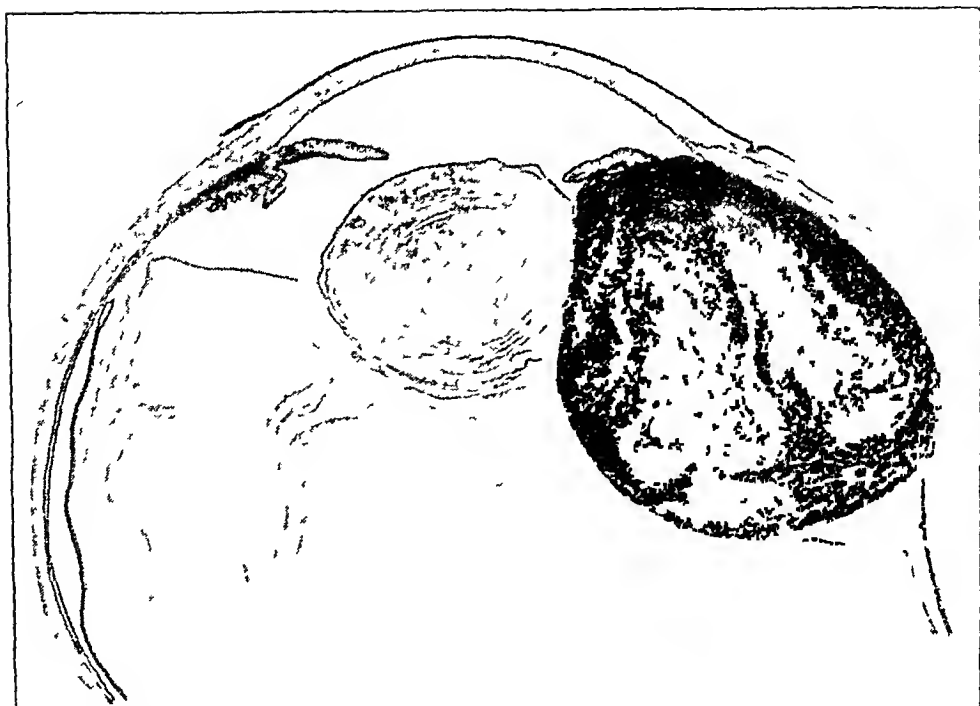


Fig 4—Absorption of lens at the equator and posterior cortical cataract. A malignant melanoma of the ciliary body produced iridodialysis. The lens is in its normal position. The substance, and not the epithelium and capsule, has vanished in the area pressed on by the tumor. The anteroposterior diameter of the lens is increased. The capsule is thrown into folds at the posterior angle between the lens and the tumor, and in the adjoining cortex there are large cystic spaces.

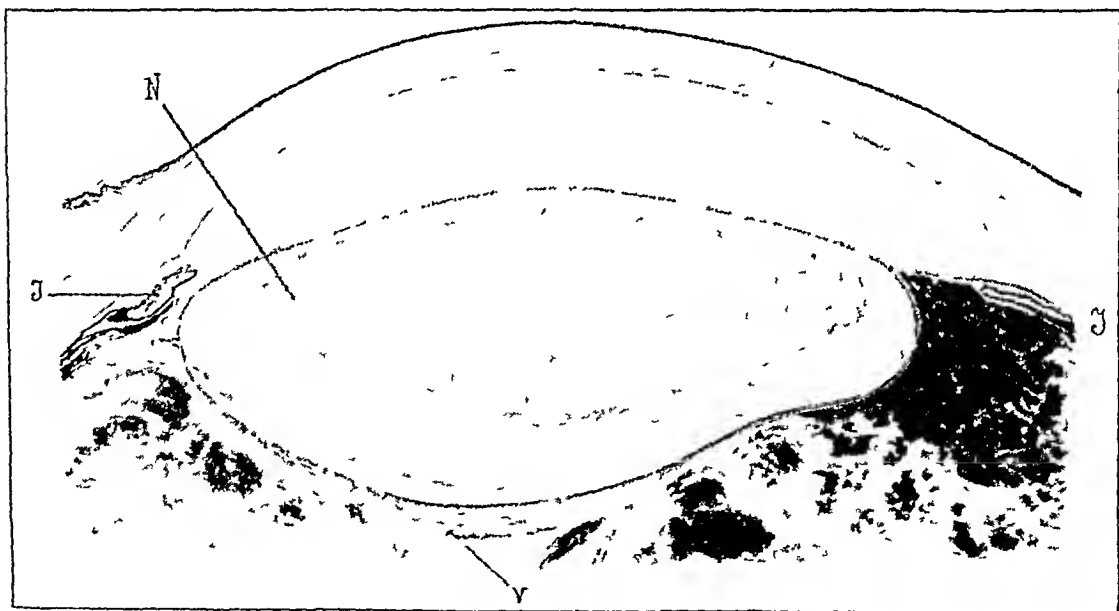


Fig 5—Morgagnian cataract in a case of retinoblastoma in a globe of a girl 1 year of age. The iris (*I*) was so shrunken that the pupil was of maximum width. In the lens, a faintly staining nucleus (*N*) is visible in a fluid cortical material, which is broader at the posterior pole. At the equator of the nucleus (*N*) there are a number of cellular elements—the remains of the germinal zone. The anterior subcapsular epithelium is in order. It disappears just behind the equator. The vitreous (*V*) lies compressed between the necrotic tumor and the lens. In spite of the child's age a nucleus is present, otherwise there would have been total liquefaction.

intense iritis and a large anterior polar cataract in association with calcium deposits in the lens could have been caused by so small a tumor. As the cataract was evidently much older than the tumor, it was concluded that iritis had antedated the tumor and was, in fact, the primary cause of the cataract. The age of the tumor could not be guessed, because in exceptional cases an intraocular tumor may not enlarge for years. Among the cases of malignant melanoma of

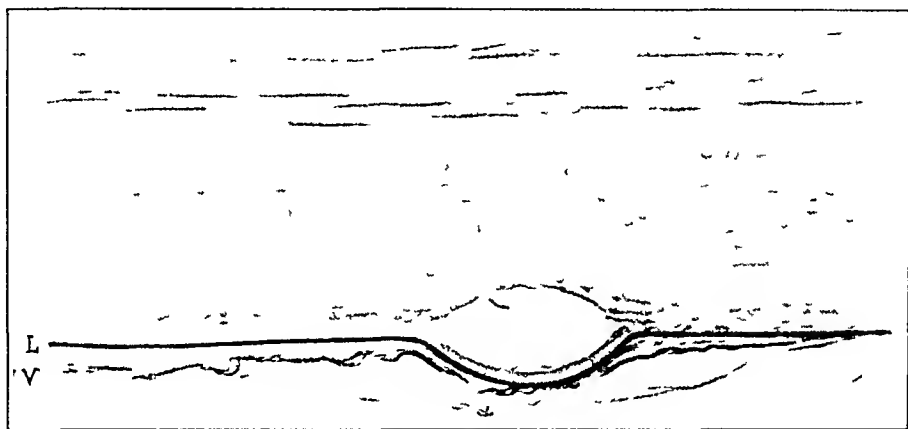


Fig 6—A curious cystic space in a case of retinoblastoma. Posteriorly a relatively large, oval cystic space is seen, filled with a slightly staining fluid. The substance of the lens separates it from its jagged walls, the posterior wall being thin. The lens capsule (*L*) is caused to bulge backward. The space has no lining. *V* represents the compressed vitreous. This formation is probably an artefact, although its fluid content takes a stain.

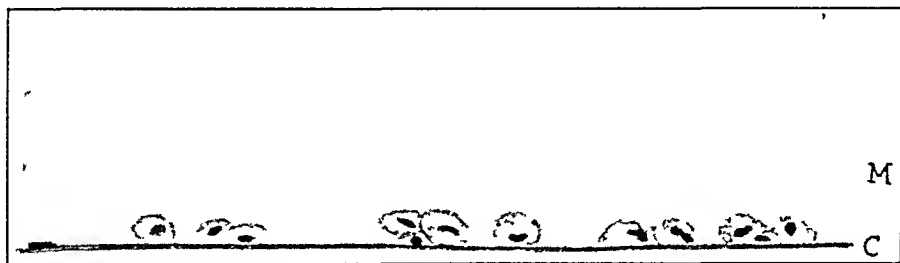


Fig 7—Phagocyte-like formations on the inner surface of the posterior capsule of the lens in a case of retinoblastoma in a globe of a boy 5 years of age. The tumor extends into the sheath of the optic nerve. The cataract is a morgagnian one. The drawing includes the posterior cortex of the lens with its capsule (*C*). The lens matter (*M*) is fluid. Lying in it, resting on the capsule, are groups of mononuclear, clear cells, containing double refracting particles, manifestly phagocytes. It would seem that in extraordinary circumstances cells on the external surface can make their way through the capsule. The fluidity of the lens indicates that there is no aperture in the capsule.

longer duration there were 2 instances of folds in the capsule worthy of mention. In the first case the globe was almost filled with a partly necrotic and perforating tumor that pressed the lens against the cornea

In association with the general necrosis of the retina and uvea, the lens capsule was dissolved at one equator, and owing to its elasticity it had withdrawn into many folds. In the second case a tumor of the ciliary body had grown against the lens, causing such distortion and decrease in its volume that for want of support the stretch of the capsule adjoining the tumor fell into folds (fig 8)

In explanation of the infrequency of folds in the capsule in the cases of tumor, it is enough to recall that a majority of the globes were glaucomatous and that with hypertony of the globe a lens has a tendency to swell and inflate the capsule, whereas with hypotony it has a tendency to shrink and let the capsule collapse

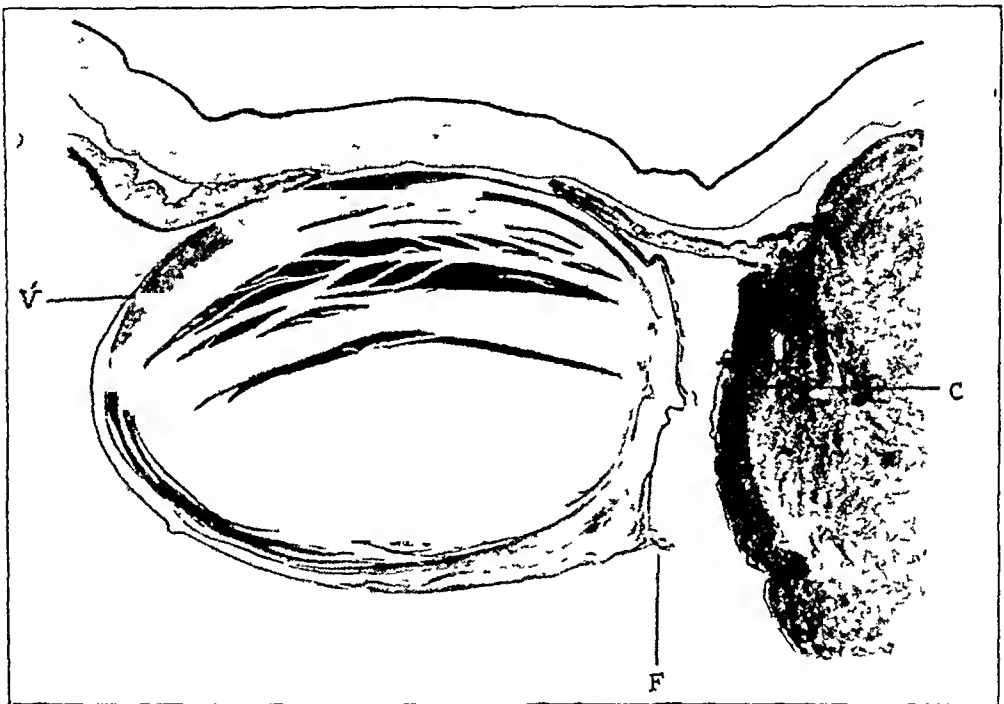


Fig 8—Vesicular cells on the side of the lens opposite that of absorption. A large malignant melanoma replaces the ciliary body and produces a wide area of iridodialysis. The collapse of the cornea is due to the fixation. A remnant of the ciliary body (C) rests on the projecting tumor. Fragments of the pigment epithelium adhering to the capsule indicate that the tumor touched the lens at the equator and caused the cortical layers to disappear under the influence of pressure. The capsule had become too large for its reduced content and therefore fell into elongated folds (F) at the point where the two bodies ceased to touch. On the opposite side of the equator a large number of vesicular cells (V) are grouped together. Here the iris shows little change.

2 Proliferation of the Subcapsular Epithelium—The outstanding change in the subcapsular epithelium in the aforementioned papers on ulcers and scars of the cornea, spontaneous iritis and detachment of the retina was one of proliferating exuberant character, often in the form of a large anterior polar cataract. However, in the cases of tumor of the present series, whenever there was any proliferation it was

as a rule restricted to a single layer of cells extending backward along the capsule. It must be due to the antagonism between distention of the capsule and proliferation of the underlying cells that anterior polar cataract is so seldom seen clinically in a glaucomatous globe. One of the few cases of anterior polar cataract was outstanding on account of the history, the anatomic changes and the uncertainty of the cause. The cataract occurred in a case of non-necrotic melanoma of the choroid that was thought to have existed for a long time because two years before enucleation a diagnosis of detachment of the retina was made. Transillumination revealed no tumor, and the age of the patient (17 years) was misleading. The globe increased in size, and an intercalary

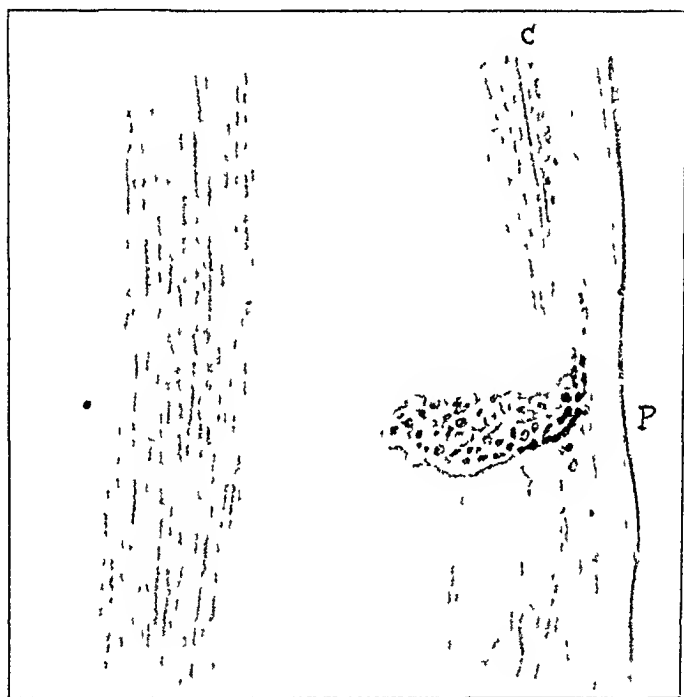


Fig 9—Desquamation and proliferation of lenticular epithelium in a case of a large necrotic malignant melanoma in a globe of a man aged 76 years. The iris, ciliary body and retina (not shown) are necrotic, as well as the cornea, which shows a ring abscess. In the fluid cortex anteriorly there is a row of desquamated cells (*C*) at one place, a sort of precipitate (*P*), composed of faintly staining hydropic mononuclear cells, extends into the depths of the liquefied lens.

staphyloma developed. Microscopic examination showed that the cataract extended under the iris far beyond the enlarged pupil. The retina was pressed against the staphyloma and the lens against the cornea. Blood vessels traversed the deep layers of the cornea. It is well known that the cornea, to the extent that a lens lies against it becomes opaque but it is not absorbed. Had the cataract been confined to the pupillary area, it might have been argued that it represented a

reaction of the cells to pressure against the hard and resistant cornea, but as so much of it was protected under the soft iris pressure was excluded as a factor. Surely the non-necrotic tumor could have played

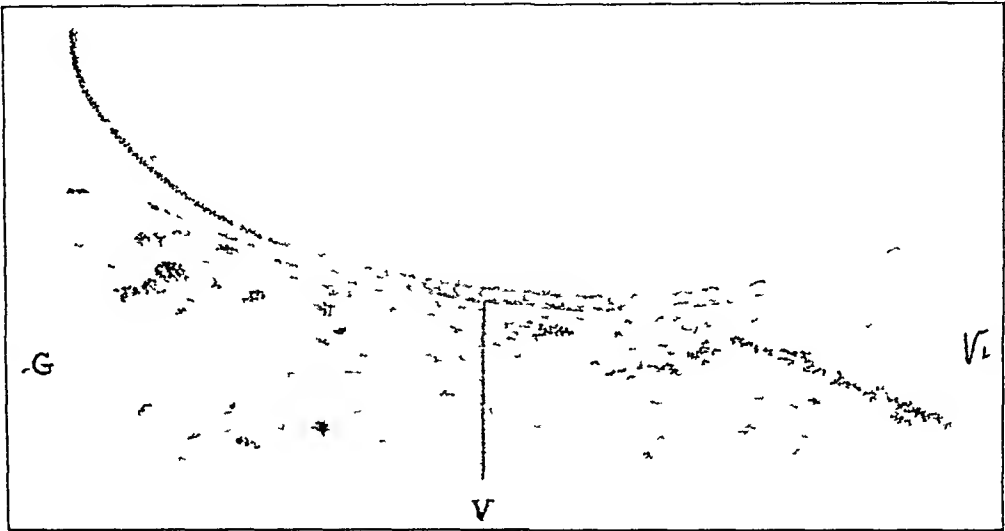


Fig 10—Subcapsular liquefaction in a case of retinoblastoma in a globe of a 4 year old child. Back of the equator a small, partially necrotic tumor touches the lens, which apparently has remained transparent. At the place of contact there is a row of oval vacuoles (*V*) lying on the inner surface of the capsule. They had undoubtedly formed in life, because they are located adjacent to the tumor and distant from it to the right there is only one vacuole. The vitreous (*V*₁) is filled with debris of the tumor, in which a few groups of nuclei represent surviving cells. To the left a wrinkled zonular fiber hangs to the lens capsule.

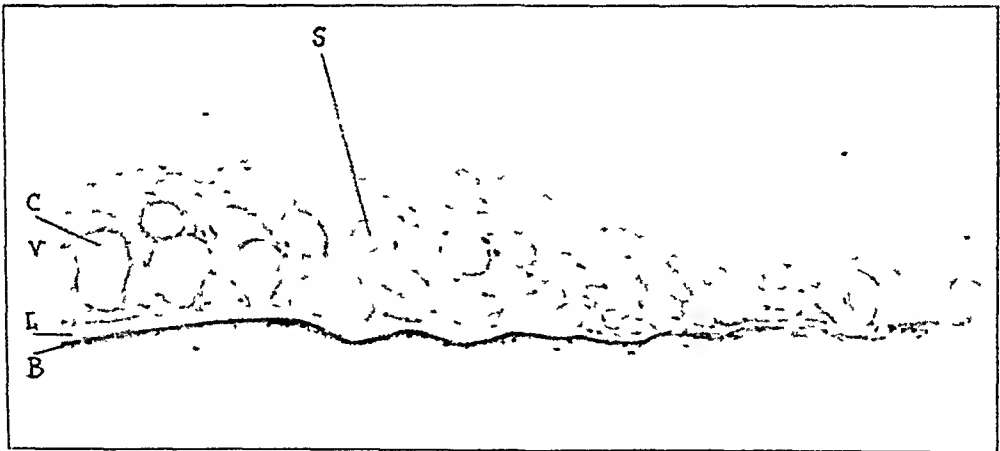


Fig 11—Vesicular cells containing vacuoles. A retinoblastoma invaded the papilla and choroid and caused the iris to shrink and the globe to enlarge. A greater part of the lens substance is cataractous. Posteriorly it is fluid. Anteriorly (not shown) there is a small subcapsular cataract. A partially necrotic tumor touches the lens back of the germinal zone which is in order. Still farther posteriorly a great number of large, oval vesicular cells (*V*) lie along the inner surface of the capsule. It is unusual that within the walls of vesicular cells there should be empty spaces (*S*) in the midst of a faintly staining fluid (*C*). The narrow, densely staining band (*B*) along the posterior capsule of the lens (*L*) represents fibers of the compressed vitreous. In the fluid back of it a few separated cells float about.

no direct role, inasmuch as it was far separated from the lens by the detached and distended retina. It may have been that toxins from the subretinal fluid irritated the cells and caused them to proliferate. The globe being glaucomatous, increased tension could have had some effect in predisposing the lens to changes. Here is an illustration of how many possibilities are to be taken into consideration when it comes to assigning a primary cause for a complicated cataract.

It is rare indeed that an intact lens capsule allows the passage of cells through it. An exception was the case of a far advanced

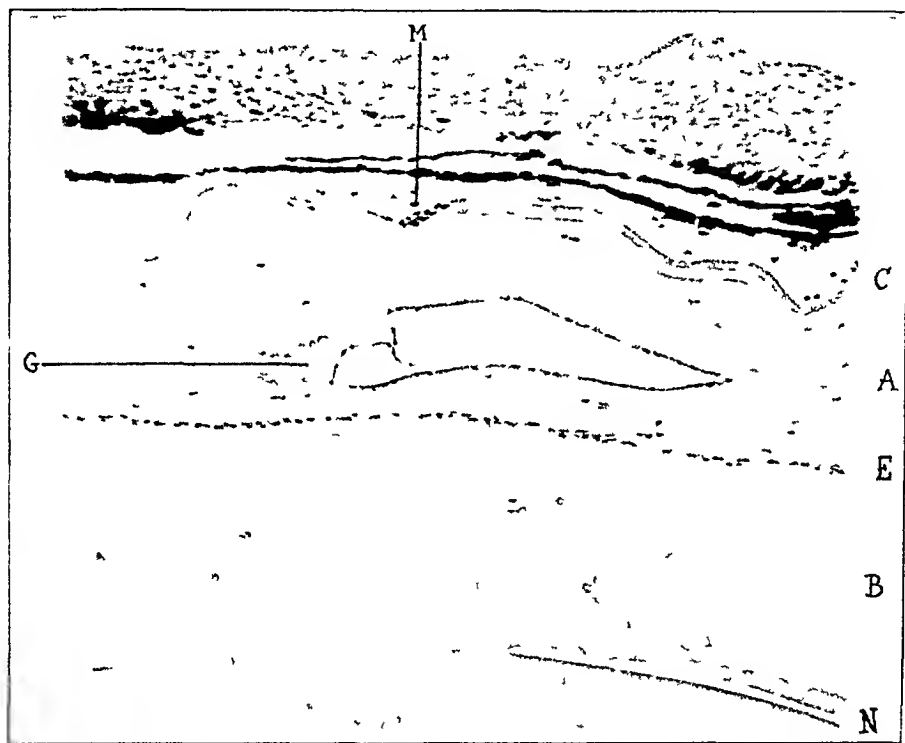


Fig. 12.—Cyst within the anterior capsular cataract in a globe of a woman aged 63. The eye had been blind for twenty years. Pathologic study reveals a partially necrotic malignant melanoma containing large fibrous membranes, as evidence that the tumor had been present for a long time. The drawing includes an anterior sector of a completely cataractous lens. The pigment layer of the atrophic iris is bound down in one area to a membrane (*M*) which fills out some folds in the capsule. A thick anterior capsular cataract (*A*), outlined posteriorly by a continuation of the capsular epithelium, detaches the wavy capsule from the lens substance proper. The cataract contains an empty cystic space, which is outlined by flat cells. To the left, globules of lens matter (*G*) are completely enclosed in the cataract. The anterior part of the cortex is fluid, but the nucleus (*N*) is homogeneous and seemingly solid. In the liquid cortex some bodies (*B*) float about, retracted from the fluid in the process of fixation.

retinoblastoma in a globe of a 5 year old boy. The lens capsule was apparently intact, distended and free of folds, and the subcapsular cells were but little disturbed. The germinal zone was gone. The sub-

stance was liquefied. Scattered in small groups along the internal surface of the posterior capsule was a row of cells that bore no resemblance to epithelial cells of the lens and, therefore, may have been phagocytes that had come through the capsule (fig 7).

In spite of the fact that proliferation of the capsular epithelium was not a characteristic of the cases of intraocular tumors, there were instances in which the restricted proliferation showed unusual features.

(a) *Druse of the Capsule* The lens in the case of the melanoma of the globe of the 17 year old girl previously mentioned showed a large druse applied to the capsule in the pupillary area. Its free surface

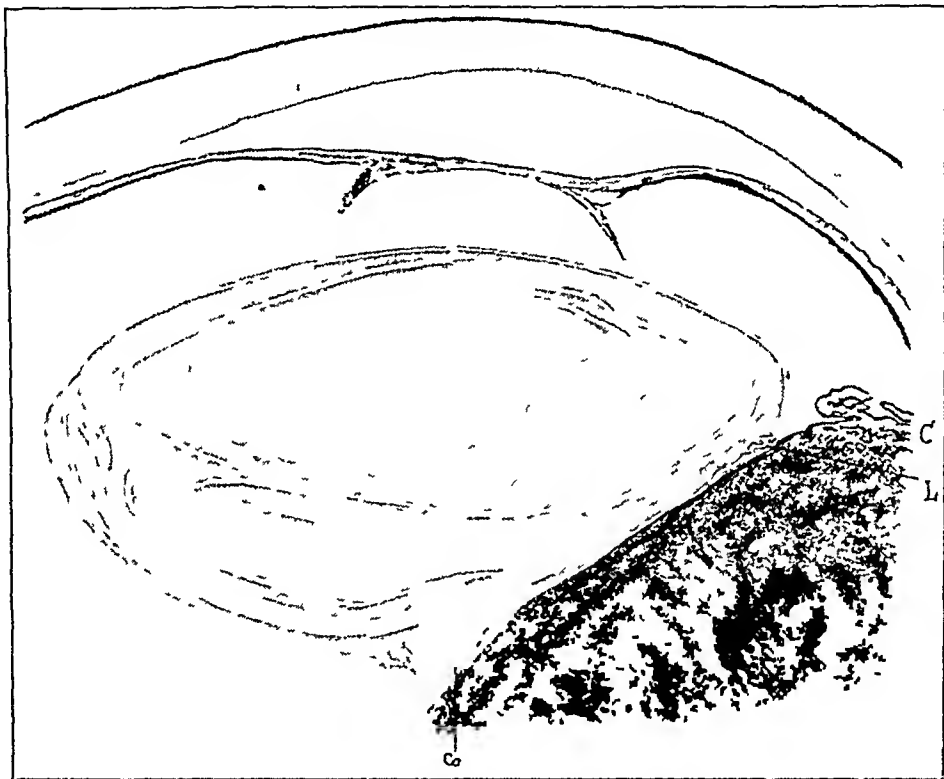


Fig 13—Cystic spaces caused by traction. A malignant melanoma of the choroid in the region of the ora serrata displaces the ciliary body forward (C) and compresses the lens. The pupil is not visible, but nearby pigmented tags from the iris approach the lens. A sector of lens matter has been absorbed along the area in contact with the tumor. The lens capsule is pressed forward at the equator (L), resulting in some ruffles. At the posterior angle of contact large cavities in the substance of the lens (Ca) are caused by traction on the capsule, which is adherent to the growing tumor. They contain a liquefied material. Nowhere else does the lens show signs of cataract.

was lined by a row of cells that had laid it down (fig 1). Only once has such a formation been encountered before.

(b) *Precipitate-Like Proliferation* Necrosis of the cornea with ring abscess and necrosis of the iris were the result of a large necrotic melanoma of a globe in a man aged 76. There was total liquefaction of the cortical substance. Some of the capsular cells had desquamated

At one point they had proliferated and arranged themselves in a cluster hanging from the capsule into the liquid cortex like a bunch of grapes (fig 9)

(c) Incipient anterior polar cataract A melanoma in a globe of a man aged 72 caused total detachment of the retina, which, in turn, pressed the lens and the iris forward. The lens appeared to be normal except for two foci of cells that lay against the subcapsular epithelium in the pupillary area (fig 15). The nuclei were compactly disposed, like those in a giant cell and their cytoplasm had no borders. These

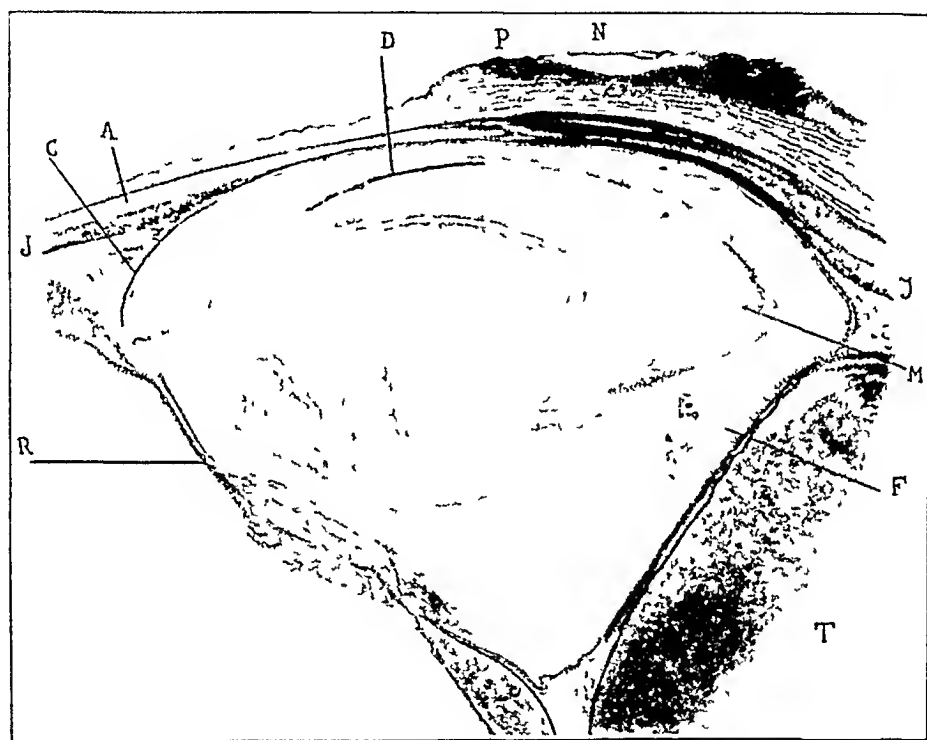


Fig 14—Morgagnian cataract and calcification in a case of retinoblastoma which involves the entire choroid (*T*) and extends into the optic nerve. The detached and degenerated retina and the tumor bulge forward to such a degree as to distort the lens into a triangular shape. The globe is buphthalmic, and an ulcer has destroyed the cornea. At *P* is the progressive border of the ulcer, with necrotic tags (*N*). The anterior chamber is slitlike (*A*). The iris (*I*) on both sides is atrophic and fixed to the lens. Behind the necrotic tag (*N*) the cornea shows a posterior abscess and pus lies in the anterior chamber. Of the capsular epithelium (*C*) only traces at the equator are to be seen. The lens is entirely cataractous. In the cortical mass of fluid (*F*) the nucleus is recognizable and forms a morgagnian cataract (*M*). On the nucleus the thinnest slivers of chalk deposit (*D*), as symptoms of a long-lasting degenerative process in the lens.

cells were smaller than the overlying capsular cells. They could not have been lymphocytes, as there was no inflammatory reaction in the neighborhood and the aqueous was free of cells. The only explanation

was that they were derived from the subcapsular epithelium and were in fact the earliest beginning of an anterior polar cataract

(d) *Cystic Degeneration of Cortex* In a case of melanoma the entire cortical substance underwent a peculiar type of cystic degeneration (fig 16) A fringe of lacelike cystic spaces enclosed the large intact nucleus, the ruffled lens capsule forming the free border Not a cell was seen in the lens, so the lens was apparently truly dead at the time of enucleation Perhaps the fixation fluids had an immediate scalding effect, blistering the cortical layers of the lens

3 *Necrosis of the Subcapsular Epithelium*—In the preparations of malignant melanomas, necrosis of the epithelium of the lens went hand in hand with necrosis of the tumor This was true even when

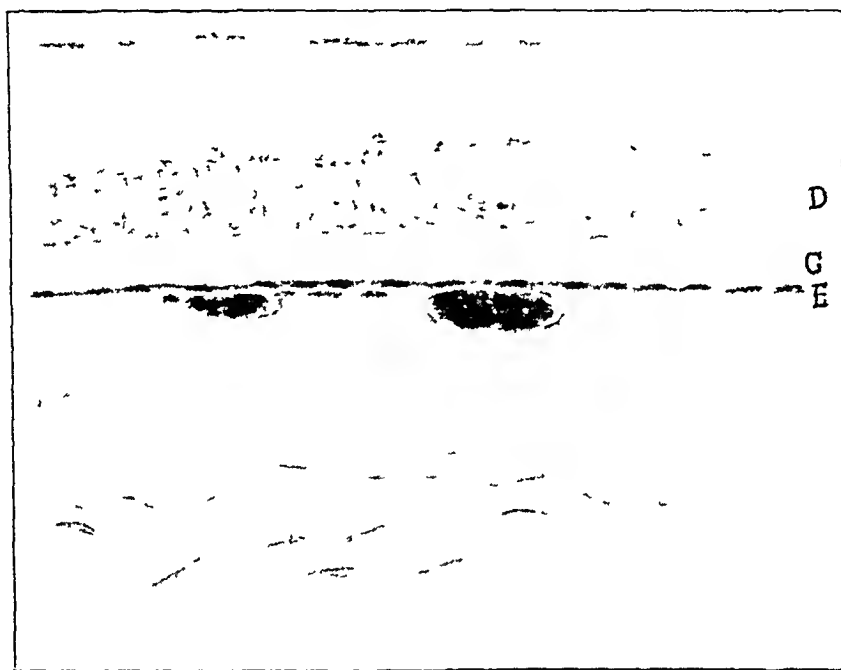


Fig 15—Early stage of anterior polar cataract in a globe of a man aged 72 years A malignant melanoma of the choroid caused total detachment of the retina The subcapsular epithelium has proliferated to form two small foci of cells (E) They resemble giant cells, as they contain many nuclei in a homogeneous protoplasm It is not possible to differentiate the individual cells The foci of cells apparently lie in cavities in the lens substance, as is suggested by the sharp border that stands out against the clear narrow zone surrounding each mass of cells Between the two foci a few shadows of nuclei under the capsule are distinguished, owing to the oblique manner of sectioning Lying on the capsule is cellular debris that originated in a deposit of albuminous fluid

the necrosis of the tumor was partial In cases of panophthalmitis produced by a totally necrotic melanoma dissolution of the lens capsule death of the epithelium and destruction of the substance are but a part of the general necrosis of the retina uveal tract cornea and sclera

A comparison of the state of the cells in the pupillary area with that of the germinal cells at the equator in the cases of malignant

melanoma revealed that not infrequently the anterior cells were preserved when the equatorial cells were gone. Altogether, the impression grew that the anterior capsular cells are more resistant to insult than the equatorial, germinal, cells. The necrotic melanomas seemed to possess greater toxicity than necrotic retinoblastomas, in other words, the uveal tumors were more destructive to the lens than the retinal tumors. Consequently, death of the lenticular epithelium to any great extent was a rarity in the cases of retinoblastoma.

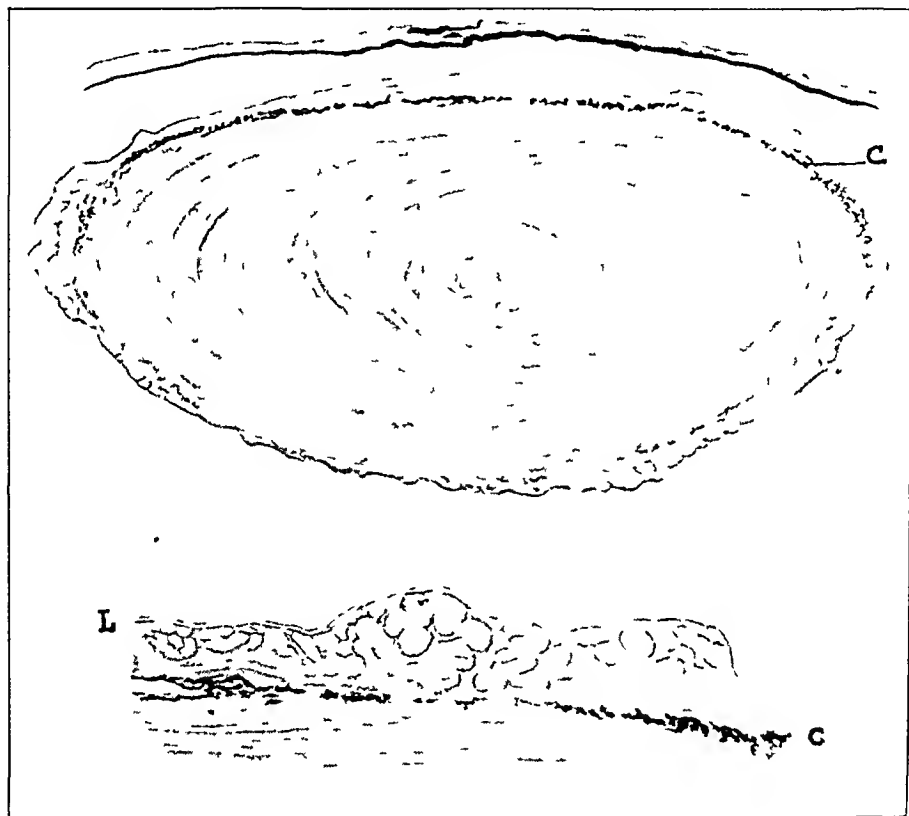


Fig 16—Lacelike cystic degeneration of the cortex and calcification of the lens in a case of malignant melanoma of the choroid. The iris is necrotic. The capsule is very wavy, but the bulk of the lens substance appears to be solid. A file of chalk granules (C) caps the nucleus anteriorly. A narrow zone immediately under the entire capsule is occupied by vacuoles of different sizes. The spaces are empty, but they do not seem to be artefacts.

The detail of the lens (L) from the anterior surface shows no capsular epithelium. The calcification is made up of relatively small granules that form a continuous row. In place of the usual homogeneous liquefaction of the cortex there is a delicate, lacelike fringe.

There were 2 glaucomatous globes in which the melanoma showed practically no necrosis but still the pupillary epithelium of the lens was gone, leaving the epithelium elsewhere unaffected. Such a condition in the pupillary area is usually caused by toxins coming directly from

the cornea. In each of these globes necrosis of the iris and the ciliary epithelium was present. It was believed that the necrosis in the three separate areas resulted from malnutrition caused by a high and sudden increase in the intraocular tension.

Illustrating universal necrosis within the globe associated with a necrotic tumor, there were 18 cases of necrosis of the iris, in 6 of which the necrosis was confined to the pupillary zone, 17 cases of necrosis of the ciliary body, in 6 of which only the processes were dissolved, and 17 cases of necrosis of the retina. It is known from other experience that, although necrosis of the ciliary body and iris occurs during an attack of acute fulminating glaucoma, the retina nearly always escapes damage. In the preceding 17 cases in which the retina was intact it was concluded that toxins from the tumor, and not glaucoma, were responsible for the disappearance of the lenticular cells.

An informative case of melanoma was one in which the death of the epithelium accurately corresponded in extent to a necrotic area of the iris that overlay it (fig. 3). The ciliary processes on the same side as the necrotic part of the iris were dissolved. The anterior chamber, containing cellular elements, was present. Three explanations as to the relation between the necrosis of the iris and that of the underlying cells of the lens come to mind. First, the iris and ciliary epithelium became necrotic simultaneously as a result of toxins from the tumor. It was true that slight necrosis was present in the tumor, but this was too insignificant to account for damage elsewhere. Second, the iris and the ciliary processes became necrotic as a result of secondary glaucoma, and then, afterward, as a result of toxins from the overlying necrotic zone of the iris, death of the subcapsular epithelium followed. Third, the necrosis of the epithelium was due to lack of nutrition from the ciliary body after the circulation had been impeded by secondary glaucoma.

As between the second and the third explanation, I prefer the second, because if really impaired nutrition had been the cause a loss of the epithelium in the pupillary area should have been found. Clinically, the globe was recorded as very hard and the iris as being of the dull gray characteristic of glaucoma. It would be well to study the effect of necrosis of the iris on the subcapsular epithelium in cases of glaucoma.

4 *Effect on the Lens of Direct Contact of the Tumor*—In the play of a tumor against a lens, it is remarkable that the lens retains its transparency even when a large part of its substance has been removed (fig. 4). This fact was first observed long ago, but even today it surprises the pathologist, not so much because lens matter disappears as a result of pressure atrophy as because the remaining lens substance does not become opaque. Anatomically, according to the preparations

pressure not only causes simple disappearance of the lens fibers but in doing so may displace and distort them and interfere with their normal development

Strange to say, in 1 of the cases of melanoma of the ciliary body, vesicular cells, in addition to the few near the tumor, were seen in larger quantity on the opposite side of the equator, as far away from the tumor as possible (fig 8). Only the lens capsule separated the hard nucleus from the tumor. Probably by way of the resistant nucleus, indirect pressure was exerted on the opposite germinal zone. A tumor, in so far as it covers the surface, must prevent the diffusion of the aqueous through the capsule and so interfere with the nutrition of the lens.

It is strange that a tumor in compressing a lens seldom produces dislocation. Apparently, a lens may more easily lose its colloid substance or become distorted than be uprooted from its attachments to the ciliary body and vitreous. This is all the more remarkable as the zonular fibers on the side of the tumor are relaxed, so that the lens can readily be shifted in the opposite direction.

5 Changes in the Lenticular Substance—Frequently cataractous changes were noted in the anterior and posterior cortex, whereas the equator, the area of predilection for senile cataract, was less often affected. In 6 of the cases of melanoma and in 1 of the cases of retinoblastoma disintegration throughout the lens was noted, that is, the substance was broken up into pieces.

Of the total number of 57 cataracts, 24 showed liquefaction in varying amounts. Eleven of these 24 cataracts were associated with retinoblastoma and 13 with malignant melanoma. In practically all the cases of melanoma the liquefaction was partial, because this is a tumor of older people, in whom the nucleus of the lens cannot be dissolved. The term "liquefaction of the lens" when applied to the young conveys the idea of fluidity throughout, when used for persons of maturer years it is understood that only the cortex is fluid. The transformation of solid lens matter into liquid form seemed to be a characteristic effect of the toxins produced in the decay of a malignant melanoma.

It was striking that in 4 of the cases of necrotic retinoblastoma, the youngest patient being a child of 1 year, faint outlines of what is known as the "embryonic nucleus" could be traced (fig 5). From this observation it was deduced first, that at this early age the embryonic nucleus as it is recognized with the slit lamp not only is an optical phenomenon but is in reality a differentiated center. This is demonstrated again in zonular cataracts, in which a distinct central opacity accurately corresponds to the embryonic nucleus. It may happen that after the

needling of a congenital cataract the nucleus appears in toto in the anterior chamber

Second, it was made clear, at least in the 4 cases, that the embryonic nucleus is more resistant than the cortex to toxins in the fluids of metabolism, otherwise it would have been liquefied

6 *Calcification of Lens Substance*—A deposition of calcium was seen in the lens in 3 of the cases of retinoblastoma. This was an impressive finding, because an intraocular tumor is rarely of such long duration as to afford time for calcification. In the first case there was a deposit of chalk along the surface of the nucleus in connection with an anterior polar cataract which was thought to have been caused by iritis that antedated the retinoblastoma. In the second case the globe was buphthalmic, and the tumor had extended to the outside, indicating a condition of long standing. In this case a crust of chalk accurately surrounded the surface of the nucleus (fig 14). In the third case, in which the condition was also of long standing, the cataract was not a typical Morgagnian one, because the cortex was not fluid but had broken up into debris. Here the chalk, also caplike, was deposited around the nucleus of the lens (fig 2). These 3 cases afford further proof that as early as the first year of life the nucleus exists as a true physiologic unit.

There was a single instance of membranous cataract. This occurred in the case of the epithelial tumor of the ciliary body which led to a dense membrane with bone in the circumlental space.

7 *Cystic Space*—A comparatively large cavity, the first of its kind observed in this series, was encountered in a case of glaucoma with a small retinoblastoma (fig 1). The lens in general deviated little from the normal. At the posterior pole a cystic space caused the capsule to bulge backward. The space was not lined with epithelium, and although it contained an albuminous fluid it was set down as an artefact. In another case, that of a mushroom-shaped melanoma, the tumor flattened the equator of the lens and, by dragging on the capsule, produced a dislocation of the fibers and with it two cavernous spaces (fig 13). In a case of necrotic melanoma in which the patient had been blind for twenty years, a flat cystic space developed, as a curiosity, near the center of an anterior polar cataract (fig 12). Finally, as a result of contact with a necrotic retinoblastoma, a row of vacuoles developed along the internal surface of the posterior capsule, giving rise to an interesting detail not described before (fig 10).

8 *Vesicular Cells*—Of the 57 cases of cataract, the lens contained vesicular cells in only 13 of the cases of melanoma and 5 of the cases of retinoblastoma, and then usually in small amounts. These cells were nearly always located in their characteristic places at the equator and

posteriorly (fig 11) Vesicular cells speak for an arrest in development of lens fibers, the causes being not so great as to destroy the cells outright

9 *Localization of the Lens*—Particular attention was paid to the location of the lens, because misplacement of itself may cause cataract In 14 cases the lens was pressed forward by a tumor that filled out the entire globe, the growth being a retinoblastoma in 2 cases and a melanoma in 12 cases There were 11 cases of forward dislocation in which the tumor was too small to fill out even half the globe Here the pressure was exerted by fluid accumulating under a detached retina In 7 cases, 2 of retinoblastoma and 5 of malignant melanoma, the lens had fallen back, owing to liquefaction of the vitreous and destruction of the ciliary epithelium to which the zonular fibers were fixed In a number of cases there was a slight dislocation to one side

10 *Tension*—The results of clinical examination were not always available, but histologically there was enough evidence for one to judge that most of the globes had been hard, or very hard, at the time of enucleation or at least had been glaucomatous at some period The question arose as to what effect, in general, the increased tension had on the production of the cataracts Taking into consideration the advanced changes in the lenses and the relatively short duration of the glaucoma, it was decided that in most cases the diminished metabolism resulting from the glaucoma did little more than predispose the lens to cataract

CLINICAL ASPECTS

In a case of ordinary cataract, considering the opaqueness of the lens, it is surprising how bright the pupil stands out by transillumination Should there be an absence of red light through the pupil when the beam of the lamp is placed at a certain place at the equator, it is probable that a melanoma of the choroid is present, provided the patient is an adult However, the lesion is by no means always a tumor since an old subretinal hemorrhage may be transformed into a large amount of pigment and thus throw a shadow On the other hand, a leukosarcoma throws no shadow In every instance in which there is a combination of cataract and glaucoma, and there is the slightest possibility of the presence of an intraocular tumor, it is advisable to recommend the removal of the globe

In a case of cataract in an infant's globe the age gives a diagnostic hint, the occurrence of retinoblastoma after the age of 4 years being exceptional In childhood metastatic ophthalmia, conglomerate tuberculosis of the choroid and, in rare cases, Hippel's disease (angiogliomatosis of the retina) may produce cataract and secondary glaucoma

Tuberculosis progresses rapidly and is not very toxic, so that usually there is not time for the development of a total cataract

The differentiation between retinoblastoma and metastatic ophthalmia is most important. If the lens is still sufficiently transparent, areas of normal retina with here and there chalky white spots look quite different from a grayish, slimy exudate behind the lens or from a smooth, organized membrane. Retinoblastoma stands out more distinctly than an exudate because the vitreous is clearer. At the same time, through the wide pupil, tremulous particles from the tumor may be visible in the circumlental space. No matter whether the lens is entirely opaque or not, the indication for enucleation of an infant's globe is not urgent so long as consensual reaction of the pupil is present. At first a retinoblastoma confines itself to replacing the retina, and therefore reliance can be put on the certain sign that as long as consensual reaction is present not all of the retina is replaced and the optic nerve is not yet involved. In every case of an infant's globe in which the pupil is wide, the lens is cataractous and glaucoma is present, particularly if the globe is enlarged or becomes so while under observation, enucleation is indicated.

SYPHILITIC UVEITIS

Diagnosis, Herxheimer Reaction and Results of Various Treatments,
Including Penicillin Therapy

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SYPHILIS AS ETIOLOGIC AGENT

SYPHILITIC uveitis¹ characteristically occurs in the secondary or late secondary stage of syphilis. When there is clinical evidence of early syphilis, a positive Wassermann reaction and prompt retrogression of the ocular inflammation after antisyphilitic treatment, the diagnosis offers no difficulty.

How valid is the diagnosis of syphilitic uveitis based solely on a positive Wassermann reaction? Or how sound is such a diagnosis in the late stage of syphilis or when the duration of the infection is unknown? What are the criteria of efficacy of antisyphilitic treatment

From the Clinic for Treatment of Ocular Syphilis, Wills Hospital

Read at a meeting of the College of Physicians, Philadelphia, Section on Ophthalmology, Dec 21, 1944

An abstract of this paper, with discussion, was published in the May 1945 issue of the ARCHIVES, page 416

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Wills Hospital

The results which have been presented in this paper must be interpreted in the light of the fact that from June 1943, the date of inception of the study, to the present time commercial penicillin has been a changing mixture of various substances. The content of "impurities" has gradually decreased as potency, in terms of units per milligram, has increased. The relative amounts of the several identified penicillin fractions, G, F, X and K, have likewise varied from time to time. These two changes, and perhaps others, suggest that therapeutic efficacy may not have remained constant and that it may be significantly different today than it was originally. It is not now possible to assess the extent to which these changes may have affected the results here reported.

1 The term "uveitis" used throughout this paper includes inflammatory processes of the anterior uveal tract clinically diagnosed as iritis, cyclitis and iridocyclitis with or without secondary involvement of the cornea. The term is used with the implication that an inflammatory process of the anterior uveal tract is not confined to one component part. Inflammation of the anterior uveal tract of congenital syphilis is not included in this study.

to justify the conclusion that uveitis was caused by syphilis? Antisyphilitic treatment exerts a nonspecific effect on uveitis

Judgment at times is difficult, since local treatment and nonsyphilitic therapy also exert a favorable action on uveitis. The purpose of this paper is to discuss these considerations, as well as the Herxheimer reaction² of the ocular lesion as evidence of syphilitic causation. The intensification of the inflammatory process (constituting the Herxheimer reaction) was evaluated with the corneal microscope and the slit lamp before and after antisyphilitic treatment. The Herxheimer reaction as observed with the biomicroscope has not been studied as a diagnostic aid.

There are no distinctive features of serous or plastic iritis to warrant the diagnosis of syphilitic causation. The nodular type is more characteristic, confusion, however, may arise with nodular iritis due to other causes, namely, tuberculosis, sympathetic ophthalmitis, sarcoidosis, severe leukemia, caterpillar hairs, leprosy and neoplasm.

Igersheimer³ stated the opinion that iritis appearing after the third year of infection should not be regarded as syphilitic unless there is a favorable response to antisyphilitic treatment. He expressed the belief that syphilis is rarely the cause of iritis in the late stage of infection. We subscribe to this opinion.⁴

It is our impression that the criteria of syphilitic uveitis used by most writers reporting on its incidence were positive serologic reactions and response to antisyphilitic treatment. Few authors have defined their criteria of diagnosis. Authors reporting on a large series of patients with syphilitic uveitis or iritis (Groenouw,⁵ Talbot,⁶ Zimmermann,⁷ Moore⁸) have included patients in the late stage of syphilis. In the

2 This well known reaction of inflamed syphilitic tissue, first described by Jarisch and later by Herxheimer, is more properly called the Jarisch-Herxheimer reaction.

3 Igersheimer, J. Syphilis und Auge, in Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 17, pt. 2, pp. 205-227.

4 Dr. Marjory K. Hardy reviewed the case records of patients who had active lesions of syphilis in various stages of the infection to determine the percentage who had inflammation of the anterior uveal tract. The result of this review follows. Primary syphilis. Of 79 patients (all males) who had a chancre observed in the presecondary stage of syphilis, none had iritis. Secondary and late secondary syphilis. Of 111 patients, 40 per cent of whom were Negroes, 4 had iritis (3.6 per cent). Late syphilis. Of 86 patients with lesions of late syphilis affecting the skin, mouth, throat or bone, none had iritis.

5 Groenouw, A., in Graefe, A., and Saemisch, T. Handbuch der gesamten Augenheilkunde, Leipzig, W. Engelmann, 1904, vol. 11, pp. 737-862.

6 Talbot, A. Recherches statistiques sur la syphilis de l'œil, Thesis, Bordeaux, no. 18, 1894.

7 Zimmermann, E. L. Syphilitic Iridocyclitis with a Consideration of Factors Influencing Its Occurrence, Arch. Ophth. 53:549-565, 1924.

8 Moore, J. E. Syphilitic Iritis, Am. J. Ophth. 14:110-126, 1931.

series reported by Moore⁸ and by O'Leary⁹ patients were included who gave no response to antisyphilitic treatment. It is doubtless this reason, and other considerations, that prompted Moore to state in his paper that confusion may arise in his group of patients with late syphilis concerning the role of this disease versus other etiologic factors.

In the study by Guyton and Woods¹⁰ of the causes of uveitis in 562 cases the etiologic role, either definite or presumptive, was attributed to syphilis in 59 cases, or 10.5 per cent of the entire series. Of these, syphilitic uveitis was present in 36 cases, choroiditis in 7 cases and generalized uveitis in 16 cases. Congenital syphilis was present in 22 cases and acquired syphilis in 37 cases.

These authors stated the opinion that with the history, results of physical examination, serologic reactions and response to antisyphilitic therapy pointing to syphilis as the cause of uveitis a positive diagnosis presented little difficulty. For this reason, the diagnosis for the greater number of syphilitic patients in their group 1 could be classified as clearcut.

Their criterion for a definite diagnosis of syphilitic uveitis were as follows: (1) a characteristic uveal lesion, with nodules or gummas, occurring in the course of either early or late syphilis but in the proper time relation to the acquisition of the syphilis, (2) a lesion which was noncharacteristic of syphilis but which occurred at the proper stage of early syphilis and responded favorably to antisyphilitic treatment, or (3) a uveal lesion which appeared as noncharacteristic but which occurred in the late stage of syphilis and responded favorably to proper antisyphilitic treatment in a patient with no other demonstrable etiologic factor.

The patients in our series, in addition to syphilis, frequently had other pathologic processes which are regarded as causing uveitis. The significance of a favorable response to antisyphilitic treatment was somewhat invalidated, since we observed that such treatment exerted a nonspecific effect (case 5).

Woods¹¹ reviewed published statistics on the etiology of uveitis. It is of interest to note that earlier authors attributed to syphilis an incidence as high as 70 per cent in cases of uveitis. More recent statistics, on the other hand, have shown a steady decrease in the incidence of syphilis (now given as from 10 to 17 per cent) and of "rheumatism," whereas the incidence of foci of pyogenic infection and of tuberculosis

⁹ O'Leary, P. A. Syphilis in Etiology of Uveitis, *Am J Ophth* **15** 24-26, 1932.

¹⁰ Guyton, K., and Woods, A. C. Etiology of Uveitis, *Arch Ophth* **26** 983-1013 (Dec.) 1941.

¹¹ Woods, A. C. Syphilis of the Eye, *Am J Syph, Gonorr & Ven Dis* **27** 133-186, 1943.

has increased with the inclusion of new causes (sarcoidosis and brucellosis)

In Woods's¹¹ study of syphilis of the eye, it is stated that iritis is by far the most important of the ocular lesions of early syphilis, that it accounts for 73.3 per cent of the total ocular complications of early syphilis and occurs in about 4 per cent of all cases of early syphilis and that in general from 30 to 40 per cent of all cases of iritis are attributable to syphilis

HERXHEIMER REACTION (THERAPEUTIC SCHOCK)

The Herxheimer reaction is the aggravation of a syphilitic lesion following the initial administration of a spirocheticidal medicament. The more acute the syphilitic inflammation, the more active the spirocheticidal medicament, the larger the dose or the more direct the method of administration that exerts greater spirocheticidal action (intravenous versus intramuscular injection), the more pronounced is the Herxheimer flare. The reaction is best seen during the secondary eruption of syphilis after intravenous injection of a large dose of an arsenical.¹²

Herxheimer Reaction After Arsenical Therapy—Soon after the advent of arsphenamine the occurrence of the Herxheimer reaction was reported with a variety of ocular lesions caused by syphilis (Flemming,¹³ Gallemaerts and Kleefeld¹⁴). Toulant¹⁵ suggested the Herxheimer reaction as a means of diagnosing syphilitic lesions of the eye. In Zimmermann's¹⁶ studies of ocular syphilis the Herxheimer reaction is

12 The reaction as originally described was a local one, an accentuation of the secondary eruption of syphilis occurring within twenty-four hours after the use of a mercurial. Its occurrence after the advent of neoarsphenamine was given as proof of the spirocheticidal action of the drug. (This applies now to the reaction occurring after the initial injection of penicillin.) Before the discovery of *Treponema pallidum* the Herxheimer reaction was used for diagnostic purposes. The reaction is attributed to endotoxins arising from massive destruction of the spirochetes. In addition to this "local" reaction, a "general" reaction was described, characterized by transitory increase in the headache of neurosyphilis and in the lightning pains of tabes. At the present time the term "Herxheimer reaction" is used in a still more general way than the "general" reaction. It was given as the explanation of the reaction in the "provocative" Wassermann test. It is used to explain local reactions other than in the original sense, for instance, a rupture of an aneurysm following administration of arsphenamine or acute yellow atrophy of the liver subsequent to jaundice and arsenical therapy.

13 Fleming. Wirkung von Salvarsan auf das Auge, Arch f Augenh **78**: 197-211, 1911

14 Gallemaerts, E., and Kleefeld, G. Etude microscopique de l'oeil vivant, Ann d'ocul **157**:152, 1920

15 Toulant, P. Les reactions oculaires consecutives au traitement specifique des syphilis de l'oeil. Leur valeur diagnostique, Arch d'opht **40** 215-227, 1923

16 Zimmermann, E. L. The Role of the Arsphenamines in the Production of Ocular Lesions, Arch Ophth **57** 509-530, 1928

discussed. He recognized three expressions of the reaction involving the anterior uveal tract (1) as uveitis in an eye previously free from all clinical changes, (2) as an exacerbation of an old quiescent iritis and (3) as an intensification in an already acute iritis.

To our knowledge, the Herxheimer reaction has not been studied in a series of patients with inflammation of the anterior uveal tract in order to determine whether the reaction, as observed with the biomicroscope, could serve as a means of differentiating a syphilitic and a nonsyphilitic process.

In our study of the diagnostic value of the Herxheimer reaction the following patients were employed: patients whose iritis or uveitis was associated with lesions of early syphilis (these patients comprised group 1, discussed later) and a group of 36 patients consecutively seen with inflammation of the anterior uveal tract who did not have clinical evidence of syphilis. For some the Wassermann reaction was negative, for others positive. The uveitis in some was regarded as nonsyphilitic and was associated with other pathologic processes causing uveitis, such as sarcoidosis. The group also included patients with late syphilis who had had considerable antisyphilitic treatment. Such patients were included to serve as controls.

These patients were examined with the corneal microscope and the slit lamp a short time before and sixteen to twenty hours after an intravenous injection of 0.45 to 0.6 Gm. of neoarsphenamine. A comparison was made of the degrees of inflammation observed in the two examinations. The observations were correlated with the history, the clinical evidence and the result of antisyphilitic treatment. All patients with positive Wassermann reactions were given antisyphilitic treatment. The Herxheimer reaction¹⁷ was regarded as positive if on second examination it was observed that the haziness of the cornea was increased, the aqueous was more turbid and contained an increased number of inflammatory cells, corneal precipitates were increased and the iris was more swollen (cases 1, 2 and 3). Usually the intensification of the inflammatory process was decisive, leaving no doubt as to a positive reaction. In some cases the intensification was less pronounced, and in a few cases evidence of intensification was essentially an increased number of inflammatory cells and/or a greater number of corneal precipitates. One patient who had iritis associated with lesions of early syphilis was examined eight hours after the injection of an arsenical.

¹⁷ Microscopic evaluation of the Herxheimer reaction is unique. As aforementioned, the reaction is apparent macroscopically or by an increase of subjective symptoms. Although we are unacquainted with any published studies of a microscopic or histologic phase of the reaction, it necessarily follows that there is such a phase. An indurated or scarred remains of a chancre would doubtless show a histologic reaction that would not extend to gross evaluation.

At this time the Herxheimer reaction was positive. In another patient (case 1) the Herxheimer flare was abating on reexamination twenty-seven hours after it was observed. Apparently, a positive reaction can be observed from eight to about twenty-four hours after the initial injection of an arsenical. We did not determine the minimum dose of neoarsphenamine that will produce a Herxheimer reaction or the earliest period in which it is observed.

Herxheimer Reaction After Penicillin Therapy—The Herxheimer flare was not uniformly observed in the 17 patients in this series whose iritis associated with lesions of early syphilis was treated exclusively with penicillin. The absence of the reaction may be explained in some patients with severe iritis by reason of the purposely reduced doses of penicillin employed at the onset of treatment in order to modify the *force majeure* of initial large doses. However, in 1 patient the reaction was observed as an accentuation of the cutaneous eruption and in another as increased swelling of the cervical lymph nodes without ocular reaction.

In 2 patients the reaction was pronounced after increasing doses of penicillin had reached 50,000 units. With 1 of these patients this dose was then halved and treatment continued in ascending doses from this level. In the other patient there was an increase of intraocular tension when the dose of penicillin approached 50,000 units, on the third day of treatment. Injections were stopped for twenty-four hours and resumed with smaller doses.

The Herxheimer reaction of iritis treated with penicillin is detailed in the report of case 3. The intensification of the inflammation was noted on examination with the slit lamp eighteen hours after an initial injection of 10,000 units of penicillin, followed by additional doses of 10,000 units every four hours until the time of examination with the slit lamp. An additional reaction was transitory pain in the affected eye three hours after the initial injection of penicillin.

Herxheimer reactions as observed in treatment of syphilis in general are likely to be more pronounced after penicillin therapy than after other chemotherapy. This is evidence of the active spirocheticidal action of penicillin and necessitates reduced initial doses in the treatment of acute inflammatory lesions of ocular syphilis.

Status of the Herxheimer Reaction as a Diagnostic Aid—Of our patients with uveitis associated with late secondary syphilis and of the patients with iridorecivism (groups 1 and 2, later discussed) the reaction was observed in 70 per cent and was not observed in 30 per cent. Nine patients, or 25 per cent, of the 36 patients with uveitis unassociated with clinical evidence of syphilis had a positive Herxheimer reaction which was regarded as false, or not indicative of syphilitic causation. It is therefore concluded that the reaction cannot be regarded

as an absolute criterion in differential diagnosis of syphilitic inflammation of the anterior uveal tract

Is the Herxheimer Reaction Harmful? The Therapeutic Paradox—Many writers discuss the Herxheimer reaction of ocular lesions only in relation to the desirability of avoiding initial energetic antisyphilitic treatment in order to produce a more gradual subsidence of the acute phase. As aforementioned, the Herxheimer reaction is a focal flare-up of the lesion following initial injection of a spirocheticidal agent. In mild or moderately inflamed lesions of the anterior uveal tract this focal flare is not productive of harm. What is potentially harmful is the end result of continued energetic antisyphilitic treatment, which produces too rapid retrogression and causes additional damage by fibrosis in too rapid healing—this is called the therapeutic paradox.

In initiating treatment of syphilitic uveitis or iritis, we were guided by the degree of inflammation and the presence of complications. For patients with a mild to moderate degree of inflammatory reaction and without complications (the majority in this series were of this type) routine antisyphilitic treatment was employed. In these patients an initial injection of 0.45 Gm. of neoarsphenamine did not result in unfavorable end results whether or not the Herxheimer reaction occurred. Initial treatment was modified in cases of the following processes—severe plastic iritis associated with considerable or complete pupillary occlusion, hypopyon or plastic exudate in the pupillary area, broad synechias, increased intraocular pressure and the nodular type of iritis, which always tends to destruction of tissue and its replacement with connective tissue. In such cases it is necessary, in order to avoid the therapeutic paradox, that early treatment be of a mild character. Fever therapy may first be employed (consisting of three to four inductions of fever) or one or two injections of a soluble bismuth compound prior to initial injection of 0.1 or 0.2 Gm. of neoarsphenamine. Subsequently this amount is increased to a full dose.

SYPHILITIC UVEITIS REPORT OF SEVENTY-TWO CASES

Of the 72 patients, 42 were males and 30 females, 50 were Negroes, of whom 28 were males. Of the 22 white patients, 14 were males. The age range was from 21 to 63 years. Of the 72 patients, 55 had unilateral and 17 bilateral uveitis. Fifteen patients had the nodular type of uveitis¹⁸ (iritis papulosa, iritis nodulosa, gumma of the iris),

¹⁸ The node or papule of the nodular type of iritis is regarded as comparable to the papule of the secondary eruption of syphilis. Igersheimer³ stated the opinion that the longer syphilitic iritis persists, the greater the likelihood of nodular (papular) formation. The statement applies to a macular eruption of syphilis. The longer it persists the greater the likelihood of papules. In the cutaneous

the nodules were always confined to one eye, no instance of bilateral nodular iritis being seen. Nodular iritis was more frequently observed in cases of iridorecivism, being present in 7 of 12 cases, in contrast to 9 of 58 cases of iritis not of the iridorecivous type. Nodules not apparent on gross examination were observed through the corneal microscope. The nodular type has been described by a number of authors (Groenouw,⁵ Igersheimer,³ Duke-Elder¹⁹ and Woods¹¹) and need not be discussed.

Of 78 cases of syphilitic iritis reported by Igersheimer,³ the disease was bilateral in 25 and of the nodular type in 31.

Our 72 patients with uveitis were divided into three groups: (1) 53 patients with other lesions (diagnostic) of secondary or late secondary syphilis, (2) 12 patients with iridorecivism and (3) 7 patients with no clinical (diagnostic) evidence of syphilis.

Group 1—Ocular involvement was most frequently seen in the late stage of secondary syphilis,²⁰ at the time the eruption was disappearing or had almost retrogressed, or in a still later stage of mucocutaneous relapse.²¹ The predominating type of eruption was the small follicular syphilid, occurring in patches or groups. Fifteen patients had this type, and an additional 17 presented a larger type of papular syphilid. The small follicular syphilid was conspicuous among the Negro patients, who also had pronounced polyadenitis and some arthritic symptoms involving one or more joints.

evolution of syphilis following the secondary stage of syphilis the nodule, the gumma and the gummatous ulcerative lesion appear. If, in the evolution of syphilis, iritis is a part of the secondary or late secondary eruption, the next lesion, reasoning by analogy, is a destructive one, such as the gumma. According to this analogy, one would not expect iritis of syphilitic origin to appear much later than five years after infection. Beyond this period the occurrence of mucocutaneous lesions that belong in the category of secondary or late secondary syphilis is rare. This analogy applies to the skin. It does not apply to other systems, notably the nervous system. These considerations explain the greater frequency of nodular iritis in patients with iridorecivism.

19 Duke-Elder, W. S. *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1944, vol. 3.

20 Of the few patients seen before the chancre has disappeared, 1 presented a chancre on the arm. The lesion was excised and the material emulsified and injected into the testes of rabbits, in an attempt to isolate an ocular strain of *T. pallidum*. The purpose of this study was not achieved (Klauder, J. V. *Ocular Syphilis: Factors Influencing the Localization of Syphilis in the Eye*, *Arch. Ophth.* 7:268-279 [Feb.] 1932).

21 The studies of Brown and Pearce (*Experimental Production of Clinical Types of Syphilis in the Rabbit*, *Arch. Dermat. & Syph.* 3:354 [March] 1921) furnished evidence that immunologic response of the rabbit to syphilitic infection is a factor in determining ocular localization in this animal.

Other writers have emphasized the frequency of a papular type of eruption associated with iritis Zimmermann⁷ and Moore,⁸ especially, stressed the frequency of iritis in the Negro and its association with a folliculopapular syphilid, polyadenitis and syphilitic arthritis (usually of the ankles) These authors regard this association of symptoms as a clinical syndrome—a racial predisposition Our study gives emphasis to the observation of these authors

Group 2—Iridorecidivism (iridorelapse) is the occurrence of iritis after insufficient treatment of early syphilis In its biologic significance it corresponds to neurorecurrence (neurorecidivism) Soon after the advent of arsphenamine, it was thought that a few injections sufficed to effect a cure It was observed that such inadequate treatment predisposed to an increased incidence of neurosyphilis In explanation of both phenomena, it is believed that insufficient treatment of early syphilis predisposes the patient to recurrence by interference with the resistance-building mechanism

In a series of 190 cases of syphilitic iridocyclitis reported by Zimmermann⁷ there were 21 instances of iridorecidivism, and in a series of 140 cases of iritis of early syphilis reported by Moore⁸ there were 29 such instances In these series, iritis appeared after a lapse of treatment comprising for the majority of patients six or less injections of arsphenamine The interval between the lapse of treatment and the appearance of iritis varied in most cases from four to sixteen weeks

A notable feature of iridorecidivism is the likelihood of the absence of other clinical evidence of syphilis and a negative or partially positive Wassermann reaction In 68 per cent of the cases in Moore's series there was no other clinical evidence of syphilis, and the Wassermann reaction was negative in 45 per cent The history of recent lapse of treatment is an important consideration in diagnosis of iridorecidivism, this applies especially to the Negro, since syphilitic uveitis is more frequent among Negroes and they cooperate poorly in therapy of the systemic infection

Of our 12 patients with iridorecidivism (cases 2 and 4), 8 were Negroes (4 males and 4 females), and the remaining 4 were white males The previous treatment varied from five to ten injections of an arsenical or a bismuth compound, followed by a lapse of treatment ranging from four to ten weeks, except in 1 case, in which it was four months In 2 patients iritis occurred in the second eye after lapse of treatment of uveitis in the first eye In 8 patients there was no clinical evidence of syphilis, in 4 there were sparing lesions that characterize a mucocutaneous relapse The Wassermann reaction was positive in all cases, although in some (cases 2 and 4) it was less strongly positive than in cases of untreated early syphilis

Case 4 illustrates the possible serious outcome of syphilitic uveitis. The end result was blindness of one eye. The patient had two relapses (iridorecidivism), each occurring after irregular treatment. After retrogression of the nodules and the pupillary exudate, there was destruction of tissue, with cicatrization causing secondary glaucoma.

Group 3—The 7 patients in this group (6 of whom were Negroes) had positive Wassermann reactions, but clinical evidence diagnostic of syphilis was absent. Four had generalized adenopathy. The history of all gave evidence suggestive of early syphilis (such as a genital lesion, eruption, sore throat), and they were in the age range in which infection more frequently occurs. They had not received antisyphilitic treatment. These patients were among the aforementioned 36 patients with uveitis who were observed for the Herxheimer reaction.²² This reaction was positive in all the 7 patients, and there was a therapeutic response to antisyphilitic treatment. In view of these considerations and the absence of other causes, these patients are included in the syphilitic group.

RESPONSE TO ANTISYPHILITIC TREATMENT

Chemotherapy Specific Effect—In the majority of patients receiving chemotherapy, disappearance of active signs of inflammation, as evaluated by examination with the slit lamp, occurred in from two to five weeks (case 2) and (in exceptional cases) in five to seven weeks (case 1).

One patient received fever therapy, 4 fever bouts preceding chemotherapy. The iritis showed improvement before chemotherapy was instituted. Twenty-two days after onset of fever treatment the affected eye was quiescent, in this interval, in addition to fever therapy, three injections of 0.45 Gm of neoarsphenamine and one injection of bismuth subsalicylate had been administered.

An equally prompt effect, however, occurred in patients given chemotherapy alone. We see no advantage in fever therapy of syphilitic uveitis except, as aforementioned, to initiate treatment of severe processes, as already discussed. In cases of this type, however, initial reduced doses of a bismuth compound prior to injections of an arsenical serve the same purpose.

It should be emphasized that in treatment of severe inflammation of the anterior uveal tract with complicating processes disappearance of inflammation should be delayed, rather than hastened, in order to avoid, as already discussed, the therapeutic paradox.

²² It is interesting to note that of 36 patients (25 of whom were Negroes) the uveitis of 7 (6 of whom were Negroes), or 19.4 per cent, was regarded as syphilitic.

An important feature of therapeutic response, more diagnostic than the period of retrogression, is prompt improvement after the Heixheimer flare (as aforementioned, this flare-up was absent in 30 per cent of our cases). Subsequent improvement is progressive until inflammation disappears. Failure of the inflammation to subside or its recurrence provided antisyphilitic treatment has been continuous challenges the diagnosis of a syphilitic causation²³

Penicillin Therapy—Seventeen patients with uveitis associated with late secondary syphilis were treated exclusively with penicillin, except for local ophthalmologic treatment. Sodium penicillin was employed, the substance being injected intramuscularly every four hours. The total dose was 2,400,000 units, administered in eight days²⁴. This period of treatment was exceeded when early doses were more gradually increased. Initial doses, depending on the severity of the inflammatory process, varied from 10,000 to 20,000 units for the first four to six injections, except that for 1 patient with pupillary occlusion and increased ocular tension the initial dose was 5,000 units. Subsequent doses were increased to a maximum of 50,000 to 60,000 units.

Penicillin exerted a prompt effect on the ocular lesion (case 3), inflammation disappeared in from eight to fourteen days after the first injection in all but 2 patients, for whom the latter period was exceeded.

Subsequent to penicillin therapy no further antisyphilitic treatment was administered. No recurrence of ocular inflammation has been observed. The patients are still under observation, the maximum period of observation has been fifteen months. Serologic reactions have become, or are becoming, negative. There was 1 exception, the blood reagin titer decreased after penicillin treatment but subsequently increased. This increase preceded a cutaneous relapse of syphilis ten months after treatment.

23. After disappearance of the syphilitic uveitis or iritis, the chemotherapy of the syphilitic infection of patients in this study was that recommended for early syphilis—a total of thirty injections of an arsenical preparation and sixty injections of a bismuth compound. The vital importance of continuous treatment (for the first year) should be emphasized to the patient in order to avoid the occurrence of recidivous iritis.

24. It is not to be inferred that this dose and the duration of its administration will finally be accepted as proper for treatment of secondary syphilis. "How best to use it, alone or in combination with other forms of treatment, is as yet undetermined but is under organized, nationwide, governmentally sponsored study, from which definitive results may be expected to emerge" (Moore, J. E. *The Chemotherapy of Syphilis*, *Am J Syph, Gonorr & Ven Dis* **29** 185-199, 1945). For discussion of treatment and schedules, rate of disappearance of early lesions of syphilis, serologic response and reactions to penicillin, reference should be made to an article by Moore and associates (Moore, J. E., Mahoney, J. F., Schwartz, W., Sternberg, T., and Wood, W. B. *Treatment of Early Syphilis with Penicillin*, *J A M A* **126** 67-73 [Sept 9] 1944).

Nonspecific Effect of Antisymphilitic Chemotherapy and Other Treatment—It is well known that most patients with acute inflammation of the iris and ciliary body respond favorably to fever therapy, foreign protein therapy, administration of salicylates and application of heat and mydriatics. As aforementioned, we observed a beneficial effect of fever on syphilitic iritis. Possek²⁵ reported on retrogression of syphilitic iritis following fever produced by typhoid vaccine before antisymphilitic treatment was instituted. Musy²⁶ observed a beneficial effect from injections of sterile milk. Igersheimer³ stated the opinion that despite the promptness with which syphilitic iritis responds to antisymphilitic treatment it is not to be denied that at times retrogression occurs after simple local treatment, or at least after nonsymphilitic treatment. In this regard, Dianoux²⁷ reported on the disappearance of syphilitic iritis after local treatment and large doses of acetylsalicylic acid.

The following case illustrates the difficulty in evaluating the significance of a positive Wassermann reaction and a favorable response to antisymphilitic treatment when such treatment had been administered. The patient was in the late stage of syphilis without clinical evidence of the disease. The Wassermann reaction was 4 plus. He had iritis with hypopyon and pupillary exudate. After local treatment, three fever bouts (typhoid vaccine) and extraction of two infected teeth, the inflammatory process retrogressed in two weeks. Visual acuity improved in this time from perception of hand movements at 1 foot (30 cm) to 6/12. Antisymphilitic treatment was purposely withheld.¹⁰

Igersheimer³ further stated the opinion that syphilitic iritis may heal in the absence of treatment. One patient in our series presented himself when iritis of the second eye appeared. The involvement of the first eye had almost disappeared in the absence of any treatment.

Antisymphilitic treatment (arsenicals, mercurials, bismuth, iodides) may exert a nonspecific effect on inflammatory processes of the uveal tract. In 14 patients reported on by Moore⁸ who were treated for nonspecific effect of antisymphilitic treatment, improvement as well as retrogression resulted provided treatment was sufficiently prolonged.

Benedict and O'Leary²⁸ stated the following opinion:

Treatment for syphilis, including the combined use of arsphenamine, mercury and iodides, has a marked beneficial influence on inflammatory conditions in the uveal

25 Possek, R. Versuche zur Behandlung luetischer Augenerkrankungen mit unspezifischen Heilmethoden, Wien klin Wchnschr **32** 743-756, 1919.

26 Musy, cited by Stocker, F. Parenteric Injections of Milk in Eye Diseases, Am J Ophth **3**:58, 1920.

27 Dianoux. Syphilitic Iritis and Aspirin, Clin opht **23** 147-148, 1919.

28 Benedict, W. L., and O'Leary, P. A. The Use of Antispecific Remedies in the Treatment of Diseases of the Uveal Tract, Tr Pacific Coast Oto-Ophth Soc. **10**.44-51, 1922.

tract When these are due to syphilis, the effect is naturally more pronounced than when syphilis is not a factor, but the effect on nonsyphilitic uveitis is none the less gratifying

They further wrote

Uveitis occurring in conjunction with tuberculous lesions and tuberculids responds very satisfactorily to treatment for syphilis

They reported that in 1 patient arsenical and mercurial therapy, given for six weeks, caused retrogression of nonsyphilitic anterior and posterior uveitis Lucic²⁹ reported that 10 patients with inflammatory processes of the anterior uveal tract of nonsyphilitic origin responded favorably to neoarsphenamine

In our experience, the nonspecific effect of antisyphilitic treatment is not uniform Injections of an arsenical and/or a bismuth preparation may in an occasional patient (case 5) cause disappearance of inflammation of the anterior uveal tract in a manner comparable to the specific effect of such treatment The nonspecific effect, however, is not always lasting

COMMENT

It becomes apparent that the Wassermann reaction, the Herxheimer reaction and the therapeutic response to antisyphilitic treatment are not infallible criteria in the diagnosis of syphilitic uveitis Since a direct diagnosis cannot be made clinically and histologic examination or demonstration of *T pallidum* is not possible, diagnosis is essentially made by a positive matching or a negative excluding process We believe the three most important criteria are (1) demonstration of, or evidence pointing to, an early stage of the syphilitic infection, (2) an inflammatory process of such character as to exclude as far as is possible other etiologic factors, (3) prompt effect of antisyphilitic treatment

PROGNOSIS OF SYPHILITIC UVEITIS FINAL VISUAL ACUITY

Visual acuity after subsidence of the inflammatory process was determined in 50 of the 72 patients The total number of affected eyes in the 50 patients was 61 Of the 61 eyes, the final visual acuity, in some with correction, in others without correction, was as follows 6/6, 21 eyes, 6/9, 21 eyes, 6/12 to 6/21, 13 eyes, 6/30, 1 eye, 4/60, 2 eyes, 6/60, 2 eyes, nil, 1 eye Secondary glaucoma occurred in 3 patients

The patient who was blinded in one eye (case 4) had vision of 6/9 in the other, previously affected, eye Another patient who had bilateral involvement had final vision of 6/60 in each eye At onset of treatment he had pupillary occlusion of both eyes and secondary glaucoma in one

²⁹ Lucic, H Neoarsphenamine in the Treatment of Nonsyphilitic Inflammation of the Uveal Tract, *Arch Ophth* **15** 826-832 (May) 1936

eye It is to be expected that iridectomy will improve this visual acuity Excluding this possibility, he is the only patient who is industrially blind It is apparent from this study that good results are obtained in treatment of syphilitic uveitis (associated with acquired syphilis) and that this form of syphilis of the eye plays a minor role in blindness caused by syphilis³⁰

ILLUSTRATIVE CASES

CASE 1—*Bilateral iritis, positive Herxheimer reaction, response to antisyphilitic treatment*

A white man aged 63 when first seen had bilateral plastic iritis of two months' duration He presented a disappearing macular eruption of syphilis The Wassermann reaction was 44440 Examination with the slit lamp microscope was made before and after the first injection of neoarsphenamine For the sake of brevity, only the results of examination of the right eye will be given Examination before injection of an arsenical disclosed generalized faint haziness of the cornea with wrinkles in Descemet's membrane, and a large number of old and some still active corneal precipitates The aqueous was slightly turbid and contained several cells The iris was somewhat dull, and there were no nodules There were pigment granules on the anterior surface of the lens Examination eighteen hours after injection of 0.45 Gm of neoarsphenamine showed an increased haziness of the cornea, the corneal precipitates were more pronounced, and there were more cells in the aqueous Reexamination forty-five hours after injection of the arsenical showed that the aqueous was slightly clearer and contained only an occasional cell Examination two weeks later showed decided improvement in the iris There were no signs of active inflammation on examination five weeks after onset of treatment In the interval, five injections of 0.45 Gm of neoarsphenamine had been administered A soluble bismuth compound was given conjointly with the first two injections of the arsenical

CASE 2—*Iridocyclitis, positive Herxheimer reaction and response to antisyphilitic treatment*

A Negro was first seen January 10 with acute iridocyclitis of the right eye of two weeks' duration The previous August he had had a chancre and secondary eruption The Wassermann reaction was 4 plus He received ten injections of from 0.3 to 0.4 Gm of neoarsphenamine, until November 18 He then allowed treatment to lapse

Examination disclosed no evidence of syphilis The Wassermann reaction was 44000 Examination with the slit lamp microscope sixteen hours after the initial injection of 0.45 Gm of neoarsphenamine showed that the cornea was more hazed than before injection There were more debris and corneal precipitates on the posterior surface The aqueous was more turbid and contained more inflammatory cells The swelling of the iris was more pronounced After the patient had received four injections of 0.6 Gm of neoarsphenamine in the course of twenty-nine days, examination with the slit lamp showed no evidence of inflammation

CASE 3—*Therapeutic response to penicillin therapy*

A Negress aged 21 was first seen May 13 with acute iritis of the right eye of one week's duration and a maculopapular eruption of syphilis of two weeks'

³⁰ This emphasizes the outstanding role of interstitial keratitis and optic nerve atrophy in the generally stated 10 to 15 per cent of all cases of blindness attributable to syphilis

duration Dark field examination of material from condylomas on the vulva gave positive results The Wassermann reaction was 4 plus, the titer was 128

In addition to local ophthalmic treatment, penicillin (sodium salt) was given intramuscularly every four hours (around the clock) for eight consecutive days The total dose was 2,400,000 units The initial doses were purposely reduced to 10,000 units for the first four injections in order to avoid too pronounced a Herxheimer flare, succeeding doses were increased by 10,000 units up to maximum doses of 60,000 and 50,000 units, in order to give the total desired amount in eight days Three hours after the first injection the patient complained of pain in the affected eye, which soon disappeared

Examination with the slit lamp microscope was made before and eighteen hours after the first injection In this interval 60,000 units of penicillin had been administered The second examination showed more pronounced corneal precipitates than did the first The aqueous was more turbid and contained a greater number of floating cells In general, there was more evidence of inflammatory reaction

Subsequent examinations showed gradual subsidence and complete disappearance of the inflammatory process twelve days after the initial injection Visual acuity before treatment was 6/9—3 and subsequently became 6/6—2 Fifteen days after initial treatment other lesions of secondary syphilis disappeared The titer of the Wassermann reaction was decreased to 32 and still later to 0

CASE 4—Iridorecidivism occurring twice after lapse of treatment, with subsequent blindness in one eye

A white man aged 25 was first seen Nov 20, 1939 He had had a chancre in September 1939, for which he received five intravenous injections He allowed further treatment to lapse Two weeks prior to the time we first saw him, the left eye became inflamed, and soon thereafter the right eye was involved

On his admission there was no evidence of syphilis The Wassermann reaction of the blood was 32100 The patient presented bilateral iritis There were nodules on the iris of the right eye, and in the left eye a plastic membrane in the pupillary area was attached to the iris and the lens Visual acuity was 5/60 in the right eye and was limited to counting fingers at 6 inches (15 cm) in the left eye

From Nov 20, 1939 to Jan 15, 1940 he received fever therapy—seven intravenous injections of typhoid vaccine and seven weekly injections of neoarsphenamine, 0.45 Gm He let treatment lapse on Jan 15, 1940 At that time the right eye was quiescent There had been a rapid retrogression of the inflammatory process of the left eye, the cornea was faintly hazy The aqueous was faintly hazed and contained a few inflammatory cells, the iris was markedly disorganized, with atrophy of the entire stroma and posterior synechias, there were opacities of the lens and numerous white opacities in the vitreous

The patient returned in November 1940 The right eye was normal, visual acuity was 6/9—2 The iris of the left eye showed destruction, thinning and atrophy The pupil was eccentrically oval, there were posterior synechias and a capsular cataract Intraocular tension was 66 mm (Schiotz), and visual acuity was limited to counting fingers A basal iridectomy was performed Thereafter the patient attended the clinic regularly, until discharged from antisyphilitic treatment The final visual acuity of the left eye was nil

CASE 5—Acute anterior uveitis with hemorrhagic retinitis, nonspecific effect of antisyphilitic treatment

A Negro was first seen in May 1944 with bilateral uveitis of eighteen days' duration The previous January he had had a chancre and secondary eruption The Wassermann reaction of the blood was 4 plus He thought that he had

received fourteen intravenous injections of neoarsphenamine. He allowed treatment to lapse for the equivalent of three injections, two of which were in consecutive weeks in April.

Examination disclosed no evidence of late secondary syphilis. The Wassermann reaction was 30000. The titer was 1 (in cases of acute untreated secondary syphilis it is about 130). Examination with the slit lamp microscope showed haziness of both corneas with corneal precipitates. The aqueous of both eyes was turbid and contained inflammatory cells. Both irises were dull. There were multiple nodules on the right iris. Broad synechias were present in the right eye, and the lens of this eye was hazed, with numerous opacities of coronary type and considerable pigment on the anterior capsule. There were numerous small exudates in the macular area of each retina and several small scattered hemorrhages. Visual acuity was limited to perception of hand movements in each eye. In addition to local ophthalmic treatment, two injections of a soluble bismuth compound and one injection of 0.3 Gm. of neoarsphenamine were given. Two weeks later examination with the slit lamp showed complete retrogression of the uveitis. Visual acuity was 6/30 in each eye.

The patient returned to the clinic in August 1944. Antisyphilitic treatment had been continuous. Examination (both eyes) with the slit lamp showed slight turbidity of the aqueous and old corneal precipitates and synechias, there was a complicated cataract in the left eye. Ophthalmoscopic examination of the right eye disclosed massive opacities and a dustlike haze in the vitreous, little detail could be seen except that in one peripheral area there was choroiditis with a small hemorrhage. In the left eye only a faint red reflex could be seen. The Mantoux test gave a questionable reaction to tuberculin in a dilution of 0.00002 and a strongly positive reaction in a dilution of 0.0001. Visual acuity was 6/9 in the right eye and was limited to perception of hand movements in the left eye. As the vitreous cleared, more hemorrhages were seen in the vitreous and in the retina, as well as retinitis proliferans. A diagnosis of Eales's disease was then made.

1934 Spruce Street

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RETICULUM CELL SARCOMA OF THE CONJUNCTIVA

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TUMORS of the hematopoietic system of the conjunctiva are lymphomas, representing an extensive hyperplasia of the lymphoid tissue, either with or without constitutional disease. Tumors of the first type, associated with constitutional disease, are usually unilateral, those of the second type are bilateral and often symmetric. The changes are so well known that it would be pointless to recapitulate the literature. In a second group, the lymphosarcomas, there is evident malignancy, they are clinically soft, rapidly growing tumors and tend to spread through the lymphatics. The histologic appearance approaches that of the benign lymphomas, consisting of small round cells, with occasional larger reticulum cells.

A perusal of the literature dealing with involvement of the lymphatic system shows that as far back as a hundred years ago Hodgkin described a condition affecting the lymph nodes and the spleen. Numerous later investigators delimited distinct entities, such as leukemia and aleukemic leukemia, and Kundrat¹ separated lymphosarcoma from the general group, finally, the terms "reticulosis" and "reticulosarcoma" appeared, characterized histologically by the presence of cells in reticular arrangement.

Lymphosarcoma is distinct from Hodgkin's disease in that it arises in one group of lymph nodes or in any aggregate of lymphoid tissue, spreading to other groups of nodes, is highly malignant and spreads apparently by the way of the lymphatics. It affects males twice as often as females and occurs at almost any age, but more frequently in the fifth and sixth decades of life. Its course is comparatively slow but fatal. The multiple appearance may suggest metastasis, but it probably represents secondary involvement due to widespread operation of the unknown existing cause within the lymphatic system. Lymphosarcoma is a systemic disease, but, according to Boyd,² the spread seems to be continuous, while in Hodgkin's disease it is interrupted. Often pro-

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1 Kundrat. Ueber Lymphosarkomatosis, *Wien klin Wchnschr* 6 211 and 234, 1893.

2 Boyd, W. A. *Textbook of Pathology*, ed 4, Philadelphia, Lea & Febiger, 1943.

gressive secondary anemia or relative or absolute lymphocytosis occurs, again, an increase of the polymorphonuclear leukocytes may be present. There is a distinct tendency to break through the capsule and invade the surrounding tissues, with fusion of groups of nodes. Necrosis occurs relatively more rarely than in Hodgkin's disease. In lymphosarcoma or malignant lymphocytoma there is complete replacement of the mature lymphocytes with much larger hyperchromatic cells, which have a small amount of basophilic cytoplasm and a round or oval nucleus with fairly prominent nucleolus. The uniformity of the cell type is striking, mitoses are present but are not easy to recognize. The individual cell is distinctly smaller than the cell of reticulum cell sarcoma, and there is no increase of reticulum as seen with silver stains. Only the original content of fibers within the node can be demonstrated, and even the amount seems to be decreased, owing to dispersion by the infiltration of neoplastic cells.

Reticulum cell sarcoma is regarded as a form of lymphosarcoma. Roulet³ attempted to link up the immature, or reticular, form of lymphosarcomatosis with the sarcomas. He based his conclusions on the concept that lymph nodes possess two types of stroma, the one consisting of fibrous connective tissue, from which the true fibrosarcoma, or spindle cell sarcoma, may be derived, and the other represented by the reticulum cell framework, from which may arise the reticulum cell sarcoma, or "Retothelsarkoma" as he designated it. According to Hallstrom,⁴ reticulum cell sarcoma starts with indolent enlargement of the lymph nodes, usually in the upper half of the body. Early, and especially distant, metastasis occurs. The hard consistency of the early stage changes to soft through degeneration in the center. Rapid growth of the tumor with early death is common, in one third of the cases death occurs within the first year. There may be a rise in temperature and anemia, with depression of the red cell count, the leukocyte count usually remains normal, an increase is present in 50 per cent of cases but does not exceed 20,000. In the early stages lymphocytosis, and in the late stages lymphopenia, has been observed. The number of eosinophils and basophils is unchanged, the monocytes occasionally show a slight increase.

If the tumor occurs in the lymph node, often no distinction is made between lymphosarcoma and reticulum cell sarcoma, this is permissible in the case of lymph nodes, the tumor arising from the reticulum cells of the node. But the last decade has taught that the tumor may originate

3 Roulet, F. Das primäre Retothelsarkom der Lymphknoten, *Virchows Arch f path Anat* **277** 15, 1930, Weitere Beiträge zur Kenntnis des Retothelsarkomas der Lymphknoten und anderer Lymphoiden-Organen, *ibid* **286**.702, 1932.

4 Hallstrom, L. Retikelzellensarkom unter dem Bilde akuten Strumitis, *Chirurg* **14** 503, 1942.

in various organs, including bone, where it forms a variety of sarcoma of bone, and therefore the designation of reticulum cell sarcoma seems more appropriate

The cells of the reticulum cell sarcoma are distinctly larger than those of the lymphosarcoma. The cytoplasm is usually abundant and faintly acidophilic, the nucleus is twice the size of the lymphocyte and is commonly constricted, giving a reniform appearance. Boyd² emphasized as highly characteristic the presence of pseudopod-like processes of the cytoplasm and the nucleus, indicating ameboid activity of the living cell. According to Oberling,⁵ the tumor is formed by syncytial masses of undivided or slightly fenestrated protoplasm, the limits of which are ill defined, and these masses are connected with zones of more or less differentiated lymphoid tissue. The fenestration, by exaggerating the internuclear spaces, may result in reticular structures. The nuclei, which are round or oval, are irregularly distributed, and the well defined nuclear membrane, sparse chromatin granules and darkly stained nuclear membrane may produce the impression of empty nuclei. Multinucleated cells have been described frequently. The tumor cells often invade the wall of veins, causing constriction or closing of the lumens. The pathognomonic feature, stressed by almost every one, seems to be the distribution of reticulum as seen in silver preparations. In addition to the general increase of reticulum, the argentaffin fibrils exhibit an intimate relationship to the tumor cells, encircling groups of cells and sending fibrils between and around the cells. The picture presented by the silver method demonstrates a variable reticulum, either a dense network or only scattered, delicate fibers. Mitotic figures are frequent. Vascularization is rich, in the form of small vessels, some of them without independent walls. The characteristics are visible only in properly fixed (to prevent distortion by shrinkage) and silver-stained material. The reticulum cell sarcoma is the most undifferentiated form of lymphoid tumors, the masses of syncytial cells reproduce the primitive character of mesenchymal syncytium, with the nuclei keeping their embryonal character. Reference has been made to cases in which reticulum cell sarcoma preceded or accompanied monocytic leukemia.

In order to provide an understandable concept of the changes in proliferation of the cells of the reticuloendothelial system, a primary consideration of the anatomic and physiologic data available cannot be omitted.

The first component of the system to attract attention was the cell designated by Ranvier as the clasmatocyte. He described phagocytosis

5 Oberling, C. Les reticulosarcomes et les reticulo-endotheliosarcomes de la moelle osseuse (sarcomes d'Ewing), *Bull Assoc franç p l'étude du cancer* **17** 259, 1928

by certain connective tissue elements which were distinct from the ordinary fibroblasts. These phagocytic cells were studied by numerous investigators, each of whom applied a different name to them. In this way, they came to be known variously as macrophages (Metschnikoff), adventitial cells (Marchand), resting wandering cells or polyblasts (Maximow) and, since they play an important role in inflammations, phagocytes. Ribbert⁶ was the first to observe their capacity of vital staining with lithium carmine. The application and injection, respectively, of colloidal solutions of acid aniline dyes (trypan blue, pyrrhol blue) intravitaly by Goldman⁷ proved that certain cells take up the dye in granular form while others do not. Aschoff and Landau, and later Aschoff and Kiyono,⁸ popularized the concept of the reticuloendothelial system, which includes all cells which when living are capable of taking up dyes and are therefore phagocytic. These cells include the reticuloendothelial cells proper, the histiocytes and the monocytes.

The reticuloendothelial cells proper are present in hemopoietic organs, i. e., bone marrow, spleen, liver and lymph nodes. They are highly phagocytic, detain foreign particles passing through the organ and take up vital dyes and india ink during life. Ordinarily endothelium of vessels remains unaffected in spite of the circulating solution of the dye. Possibly the germinal cells of lymph nodes belong to this first group of the reticuloendothelial system. The histiocytes, or wandering phagocytic cells of the tissues, the adventitial cells of the vessels, which play important part in the inflammations, form the group of histogenous cells. They are found in all organs, not in the hematopoietic system alone. The monocytes, the last group of the system, are the white blood cells derived from endothelial elements of the reticuloendothelial system. They are important phagocytic cells, known by such diverse names as the large mononuclear and transitional cells of Ehrlich, the endothelial leukocytes of Mallory and the macrophages of Metschnikoff. Before the origin of the monocyte from the reticuloendothelial system was accepted, it was claimed that they came from the lymphocyte (Maximow⁹) or the myeloblast (Naegeli¹⁰). Quantitatively, the cells are prevalent in the hematopoietic system.

6 Ribbert, H. *Lehrbuch der speciellen Pathologie und der speciellen pathologischen Anatomie*, Leipzig, F. C. W. Vogel, 1902.

7 Goldman, E. E. *Die aussere und innere Sekretion des gesunden und kranken Organismus im Lichte der vitalen Färbung*, Beitr. z. klin. Chir. **64** 192, 1909.

8 Aschoff, L., and Kiyono, K. *Zur Frage der grossen Mononuklearen*, Folia haemat. **15** 383, 1913.

9 Maximow, A. A. *The Macrophages or Histiocytes*, in Cowdry, E. V. *Special Cytology*, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 711.

10 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, ed. 5, Berlin, Julius Springer, 1931.

The function of the cells of the reticuloendothelial system is four-fold phagocytosis, storage, formation of antibodies and blood production

The phagocytic activity is obvious, and by virtue of these cells the spleen, liver and lymph nodes are destined to be the great filters of the body, as the iron-bearing pigments of the cells in various diseases clearly testify

The storage power of the cells is manifested toward lipids, hemoglobin and iron. When lipid as cholesterol is fed to animals for a considerable time or is injected intravenously *intra vitam*, the cells are filled with the cholesterol. Hyperplasia of cells of the reticuloendothelial system associated with lipidoses belongs in this category. The lipidoses are divided by Thannhauser into cholesterosis (xanthomatosis and Hand-Schuller-Christian disease), cerebrosidosis (Gaucher's disease) and sphingomyelinosis (Niemann-Pick disease, or lipid histiocytosis). The presence of lipids within the cells may be due either to infiltration or to an inherent intracellular disturbance of metabolism within the cells.

The role of the cells in antibody formation was proved through blocking of the cells with india ink or a vital dye, resulting in diminished formation of antibodies.

The role in blood formation includes the production of both red and white cells. Monocytes are formed by proliferation of the special endothelial cells, erythrocytes, by the endothelium of the intrasinusoidal capillaries of the bone marrow. Monocytosis, or increase of the mononuclear cells through stimulation of the reticuloendothelial system, may be observed with malaria, kala azar, brucellosis, endocarditis lenta and some of the septicemias, according to Sabin,¹¹ they are the precursors of the epithelioid cells in the tubercle.

Soon after delineation of the reticuloendothelial system as a unit, attempts were made to describe the pathologic variations, tumors, whose constituent elements were reminiscent of the newly described system. The reticulum cell sarcoma is the best example of such tumors. Goormaghtigh,¹² in this *reticuloendotheliome*, described the cells of this malignant proliferation as different from the round, mobile elements of the other benign or malignant lymphoid tumors. The term "retothelial sarcoma," introduced by Roulet, has been used to designate a malignant tumor arising in the lymph nodes, the spleen or the bone marrow, and occasionally in the submucosa of the respiratory or the gastrointestinal tract. Possibly Hodgkin's disease may belong to this group, if not a tumor, it is certainly a disorder of this system of cells, a reticuloendotheliosis.

11 Sabin, F. R. Cellular Reactions to Fractions Isolated from Tubercle Bacilli, *Physiol Rev* **12** 141, 1932

12 Goormaghtigh, N. Sur la prolifération maligne du tissu réticuloendothélial des ganglions lymphatiques, *Compt rend Soc de biol* **92** 457, 1925

Ewing¹³ suggested first, in 1913, the possibility of tumors arising from the reticulum cells. Roulet³ proposed the designation *Retothel-sarcoma*, the name being shorter than reticuloendothelial sarcoma and more justified, the growth originating not in the endothelial cells of the lymph sinuses but in the cells of the network containing intraplasmic fibrils. Oberling⁵ first employed the term "reticulosarcoma" for an immature form of tumor of the bone marrow. Reticulum cell sarcoma does not represent the first stage of tumor formation but is a different form of tumor, originating in well differentiated elements of the tissues. The reticulum, having preserved the original type of mesenchymal cell, offers the possibility of mixed type tumors. Roulet differentiated three types of the tumor: the immature, the mature and the mixed type. In the immature variety the proliferation consists of small cells, 15 to 20 microns in diameter, with almost imperceptible cell contours. The protoplasm contains vacuoles, and often fat droplets. The nuclei are round or oval with chromatin-like dust, delicate particles or granules may be present, differentiation into nucleoli varies according to the maturity of the cells. Neither collagen nor a fibrillary network is visible. Transitional varieties lead from the immature to the mature form. In the latter the proliferating cells show already a pronounced tendency to form nets of argentophile fibers. The cells are polymorphic, large and oval or stellate, they are similar to the cells of the immature form but differ in the presence of short, spindle-shaped cells anastomosing through intraplasmic fibrils. Through amitotic division, giant cells, up to 75 microns in diameter, are produced, the nucleus, large in proportion to the protoplasm, occupying almost the entire cell. The fibrous network consists of parallel stripes, the fibers are thicker than in normal lymph nodes and show a tendency to collagenization. The third, or mixed, variety occurs with leukemia or Hodgkin's disease.

The reticulum cell sarcoma occurs more often in the upper half of the body and is characterized by slow growth and late metastasis or generalized involvement. Roulet had to change his opinion regarding the relatively favorable prognosis on account of the occurrence of the tumors in the abdomen and pharynx and recognized the generalized form. His original opinion that the tumor showed a slighter tendency to metastasis and a generalized form of reticulum cell sarcomatosis than does lymphosarcomatosis was not maintained by his later observations. The reticulum cell sarcoma represents a subdivision in the group of sarcomas originating in the retothelial elements of the lymphatic-lymphoid organs. The metastatic extensions of reticulum cell sarcoma are not confined to the type of tissue in which the primary tumor arose; in contrast, all types of sarcomas of the lymphoid tissue tend predomi-

13 Ewing, J. Endothelioma of Lymph Nodes, J. M. Research 28 1, 1913

nantly to limit themselves to the original type of tissue, that of the hematopoietic system. The true blastomatous nature of lymphosarcomatosis and reticulum cell sarcomatosis seems to be proved, despite the systemic character of the disease, since all the basic criteria of true malignancy are manifested in the growth.

Roulet classified the *Retothelsarkoma* into three and de Oliveira¹⁴ into six types. The types as differentiated by de Oliveira are as follows: 1. The cytoplasmic-syncytial afibrillar type. This is a pure cellular variety, the reticulum cells exhibiting a tendency to free themselves from the syncytial complex but remaining connected with the syncytium through thick cellular projections. Fibrils are absent in silver preparation. 2. The type characterized by a tendency to isolation of cells and appearance of intraplasmic argentophile fibers. 3. The fibroreticular-syncytial form, stellate cells forming syncytial nets, with well defined cell contours and pronounced reticular nets of silver-impregnated fibrils. 4. The fibrocellular form, corresponding to the mature stage of reticulum of the lymph nodes. The cells are not connected through syncytial elements but are joined by delicate projections or are free on the network. Numerous fibrils appear in silver preparations, projecting in all directions and encircling the cells, thus producing an alveolar appearance. 5. The form characterized by polymorphic cells with giant cells. 6. The type with differentiation in a hematopoietic direction. According to the dominance of lymphoid or myeloid elements, tumors of the last type are called reticulum cell lymphosarcoma and reticulum cell myelosarcoma. De Oliveira emphasized the tendency to the generalized form of the tumors and the malignant character. There is a predilection for the upper half of the body, but the tumor is often encountered in the abdomen, and in the latter case is even more malignant. The prognosis was given as unfavorable, death occurring within a comparatively short period.

The classifications of Roulet and de Oliveira are widely used, but before the work of these authors, soon after Aschoff's delineation of the reticuloendothelial system as a physiologic unit, attempts were made to describe the pathologic variations, tumors whose constituent cells were reminiscent of the elements of the sharply demarcated new system. Oberling and Oberling and Raileanu¹⁵ applied the designation *reticulosarcome*, Parker and Jackson,¹⁶ in this country, that of reticulum cell sarcoma. The classification of the Lymphatic Tumor Registry defines

14 de Oliveira, G. Ueber die Stellung der Retothelsarcome im System der Lymphdrusengeschwulste, *Virchows Arch f path Anat* **298** 414, 1936.

15 Oberling, C., and Raileanu, C. Nouvelles recherches sur les reticulosarcomes de la moelle osseuse (sarcomes d'Ewing), *Bull Assoc franç p l'étude du cancer* **21** 333, 1932.

16 Parker, F., Jr., and Jackson, H., Jr. Primary Reticulum Cell Sarcoma of Bone, *Surg, Gynec & Obst* **68** 45, 1939.

reticulum cell sarcoma as a malignant tumor of reticulocytes (monocytes) and implies its close relation to the sarcomatous form of Hodgkin's disease. The reticulum cell sarcoma represents the most undifferentiated form of lymphoid tumors. According to Warren and Picena's¹⁷ concept, the lymphoid tissue is a network of undifferentiated cellular reticulum (stem tissue), with lymphoid cells (lymphoblasts, prolymphocytes and lymphocytes) embedded in the interstices. Malignant tumors may originate in the reticulum of the lymphocytic or lymphoblastic cells, or they may be mixed, a combination in which reticulum and lymphoid cells are affected. Glogengiesser¹⁸ held that the localization, cause, prognosis and histologic structure justify the differentiation of the tumors originating in the reticulum cells from the lymphosarcomas and endothelial sarcomas, the former exhibiting the tendency to generalized appearance and infaust prognosis.

Verhagen,¹⁹ in 1940, tabulated 64 cases (31 male, 33 female), including his own. In the early stages, according to his description, the lymph nodes are very hard but painless. The tumor may originate in any lymph node and remains for a relatively long time limited to one group of nodes, later, infiltrative progress may be noticeable but is less frequent in the generalized form. Pain is due to compression of nerves or vessels of the neighboring structures. Most of the clinical symptoms are referable to the space-occupying quality or mechanical interference of the growth, but the progressive loss of weight, leading to typical cachexia, indicates the malignant nature. The progress is rapid, of 35 patients, 8 died within three months, 7 in less than nine months, 6 within one year and 11 in less than four years. The lymph nodes of the neck, axillas, tonsils and pharynx appear to be sites of predilection. The growth is most probably of multicentric origin. Primary origin in the lower half of the body prevails in females. In 50 per cent of the cases generalized involvement of all lymph nodes occurred, with the presence or absence of organ metastasis about equally distributed. Metastases frequently were found in the liver and spleen, less frequently in the lungs, kidney, adrenals and heart, they were more often encountered in the bones, especially in the spine. Metastasis was rare in the gastrointestinal tract, the brain and the uterus. The route of spread is the lymphatic vessels, but possibly the blood vessels are

17 Warren, S., and Picena, J. P. Reticulum Cell Sarcoma of Lymph Nodes, *Am J Path* **17** 385, 1941.

18 Glogengiesser, W. Generalisierte Retothelsarkomatose, *Virchows Arch f path Anat* **306**:506, 1940.

19 Verhagen, A. Ueber das Retothelsarkom in seiner histologischen und klinischen Bedeutung, *Ztschr f Krebsforsch* **50** 163, 1940. Benecke, E. Ueber leukamische Meloretikulose mit Uebergang in Retothelsarkom, *Virchows Arch f. path Anat* **306** 491 1940.

instrumental Increase in temperature is part of the picture, not only in the generalized but in the localized variety of the growth Secondary anemia is almost a constant feature, the erythrocyte count sinks to from 3,800,000 to 2,800,000, the white cell count approached normal figures only in 9 cases, being below 5,400 in 9 cases and from 8,000 to 20,000 in 18 cases In 13 cases increase of neutrophils was noted, with slight or moderate lymphopenia In the beginning the reticulum cell sarcoma responds to radiation, which gives place in a short time to renewed swelling of the original or other sites, of radiation-resistant character The primary tumor and the metastases may differ in degree of differentiation, all varieties, from the immature sarcoma to the more mature structure, with argentophile fibers and a network of fibrils, and finally, the almost mature type, with differentiation of the tumor cells in the hematopoietic direction, are occasionally represented in the same case

The formation of tumor occurs in all sites of physiologic location of lymphoid tissue and is therefore almost ubiquitous, the lymph nodes, the bone marrow and the respiratory, digestive and urogenital tracts may be the site of origin Oberling first described the growth in bones, according to Szutu and Hsieh,²⁰ the tumors of bone metastasize relatively late, in contradistinction to reticulum cell sarcomas of the soft tissues, in which the generalized spread occurs relatively early Kinney and Adams²¹ described 3 cases of primary reticulum cell sarcoma of the temporal lobe of the brain The cells of the tumor resembled and had common origin with the histiocytes, and the reticulum was formed by fibroblasts stimulated to activity by the tumor cells Owing to the fact that the histiocyte is found in any organ of the body, the tumor was described as originating, among other sites, in the thoracic wall, the thyroid, the ovary and the testis Kirshbaum, Larkin and Culver²² designated the prostate as the site of origin These authors called attention to the opinion expressed by Ewing¹³ that the normal gland does not contain adenoid tissue and, consequently, that the lymphosarcoma must be explained as anaplastic carcinoma Conversely, Symmers²³ stated the belief that the prostate gland belongs to the auxiliary lymphatic system, containing interstitial lymphoid foci, and Wegelin²⁴ maintained that in certain organs (skin, thyroid, kidney and

20 Szutu, C, and Hsieh, C K Primary Reticulum Cell Sarcoma of Bone Report of Two Cases with Bone Regeneration Following Roentgenotherapy, *Ann Surg* **115** 280, 1942

21 Kinney, T D, and Adams, R D Reticulum Cell Sarcoma of Brain *Arch Neurol & Psychiat* **50** 552 (Nov) 1943

22 Kirshbaum, J D, Larkin, H S, and Culver, A Retothel Sarcoma of Prostate Gland, *J Urol* **50** 597, 1943

23 Symmers, D Primary Lymphosarcoma of Prostate, *Arch Surg* **6** 755 (May) 1923

prostate gland) lymph follicles, although normally absent, may evolve as part of the inflammatory reaction. Jenney²⁵ observed reticulum cell sarcoma occurring spontaneously in the mesenteric lymph nodes of albino rats, the tumor was successfully transferred through twelve passages by subcutaneous implantation into animals of the same strain. The constituent cells were pleomorphic, being composed of large cells with a moderate amount of cytoplasm and large clear nuclei with one or two prominent nucleoli. Similar, but much larger, cells with two or three nucleoli were present as well as small lymphoid cells. The characteristic reticulum was composed of branching fibrils of varying thickness, distributed among the cells. Tumor transfers not only invaded the adjacent muscle tissue but led to distant metastases in the lung, liver, spleen, mediastinum, kidney and bone marrow. The inoculated tumors grew commonly more expansively than did the spontaneous variety.

The reticulum cell sarcoma shows a predilection to arise in the upper half of the body, but the unusual location of the primary tumor in tissues of the palpebral conjunctiva and the subsequent rapid expansion and death of the patient present unusual and interesting features. It seems that the case I am about to describe is the first one of its kind in the ophthalmologic literature, careful search did not reveal any other observation that could be correlated with mine.

REPORT OF A CASE

Past History—A. L., a white man aged 29, six months before admission had had an incision made on the left lower lid because of a "blood clot."

Family History—The family history in general was noncontributory.

Laboratory Data—The urine was clear and alkaline in reaction, and the specific gravity was 1.020. Occasional epithelial casts and triple phosphate crystals were noted.

The leukocyte count was 12,000, with 69 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes and 2 per cent endothelial leukocytes, the hemoglobin concentration was 108 per cent, and the erythrocyte count was 5,000,000.

The Wassermann, Kline, Frei and Mantoux tests gave negative reactions.

The evidence of gross pathologic change on roentgenographic examination of the thorax was insufficient to be of diagnostic value.

Clinical Examination—Left Eye. There was marked ptosis of the upper lid, without redness or edema. As compared with the normal (right) palpebral fissure, the left was two thirds closed. There was no pain or tenderness around the orbital margins.

The everted conjunctiva of the upper lid exhibited numerous large papillary hypertrophies. The papillae were red and seemed of firm consistency, touching them did not produce any bleeding. These papillary hypertrophies were similar

24 Wegelin, C. Ueber ein Lymphom der Prostata, Wien klin Wchnschr 48 1236, 1935.

25 Jenney, F. S. Reticulum Cell Sarcoma of Rat Transferred Through Twelve Successive Passages in Animals of Related Stock, Cancer Research 1:407 1941.

to those seen in cases of severe vernal conjunctivitis, however, they were unilateral, were present on the palpebral conjunctiva of the upper and lower lids and were much larger than are ever observed with conjunctivitis vernalis. The conjunctiva of the lower lid was equally covered with papillary hypertrophies, and in the lower fornix there was a pea-sized, round tumor-like mass.

Lymph Nodes The right preauricular lymph node was the size of a lima bean, without inflammatory symptoms, it caused conspicuous bulging of the skin, which was freely movable. Neither spontaneous tenderness nor pain on pressure could be elicited. There were slightly enlarged lymph nodes on both sides of the neck.

Treatment and Course—The clinical picture was a rare one indeed, and biopsy of the conjunctival mass was performed, followed a few days later by excision of the enlarged left preauricular lymph node.

After the biopsy, the left eye and the left preauricular region were subjected to roentgen irradiation, on Nov. 11, 1943 the patient receiving 200 r to the left eye and on November 12, 150 r each to the left eye and the left preauricular region, the same dose was given again to both areas the next day (November 13).

The patient was readmitted to the hospital on March 3, 1944.

Immediately after exposure to roentgen radiation the patient had complete closure of the lids, the upper and lower lids showed enormous swelling and redness. Eversion of the upper lid became impossible, the conjunctiva of the upper lid could not be seen, the hypertrophic projections of the lower lid showed definite retrogression. The preauricular region was normal and the scar of the incision almost imperceptible. The patient complained of excruciating pain in the back, but the physical, neurologic and roentgenologic examinations revealed nothing significant.

On March 21, 1944, the patient was discharged, with his condition unimproved.

He was readmitted three days later on account of unbearable pain in the lower part of the back.

The urine was cloudy and alkaline in reaction, and the specific gravity was 1.010.

The leukocytes numbered 3,300, with 79 per cent polymorphonuclear leukocytes and 10 per cent lymphocytes, the hemoglobin concentration was 48 per cent and the erythrocyte count was 2,310,000.

In order to relieve the pain, a 1 per cent solution of procaine hydrochloride was repeatedly injected into the painful areas, and the right posterior and pelvic regions each received eleven treatments, between March 31 and April 17, 1944, with 150 r of high voltage roentgen radiation, without any relief. Codeine could not control the pain.

About April 1 a septic temperature developed, on April 17 a systolic murmur was noted in the mitral area, on April 19 the formerly negative roentgenogram of the chest showed loss to absence of illumination over the lower third of the left pulmonary field and areas of rarefaction at the interior angle of the right scapula. The diagnosis (Dr. J. Furst) was probable neoplastic metastasis. The septic temperature continued, repeated blood cultures yielded no pathogens. On medical consultation, on April 25, no clinical signs were found in the chest. The blood picture showed 3,300 leukocytes, with 79 per cent polymorphonuclear leukocytes and 10 per cent lymphocytes, 2,310,000 erythrocytes, and 48 per cent hemoglobin. The patient had marked tachycardia with a systolic blowing sound. The possibility of osteomyelitis with discharge of septic emboli into the blood stream was suggested. On May 5 the patient showed striking euphoria. Neurologic examination revealed definite signs of multilocular impairment of the spinal cord, muscular atrophy of the middle part of the right hand, a bilateral Hoffmann sign and absence of abdominal reflexes. Only slight active movement was present in

the left leg, the right leg was completely paralyzed. The muscles of the legs were flabby, the knee and ankle jerks were hyperactive. There was evident ankle clonus, which was persistent on the left side and abortive on the right. A Babinski sign was elicited on the right. There were marked hypalgesia from the toes to the ninth dorsal segment and hyperesthesia to touch. Position sense was absent in the toes of the left foot and decreased in the toes of the right foot. Vibration sense was absent in the left foot and diminished in the right foot. The neurologic changes indicated metastasis in the cervical and dorsal portions of the spinal cord, involving the anterior horn, the pyramidal tracts and the posterior columns.

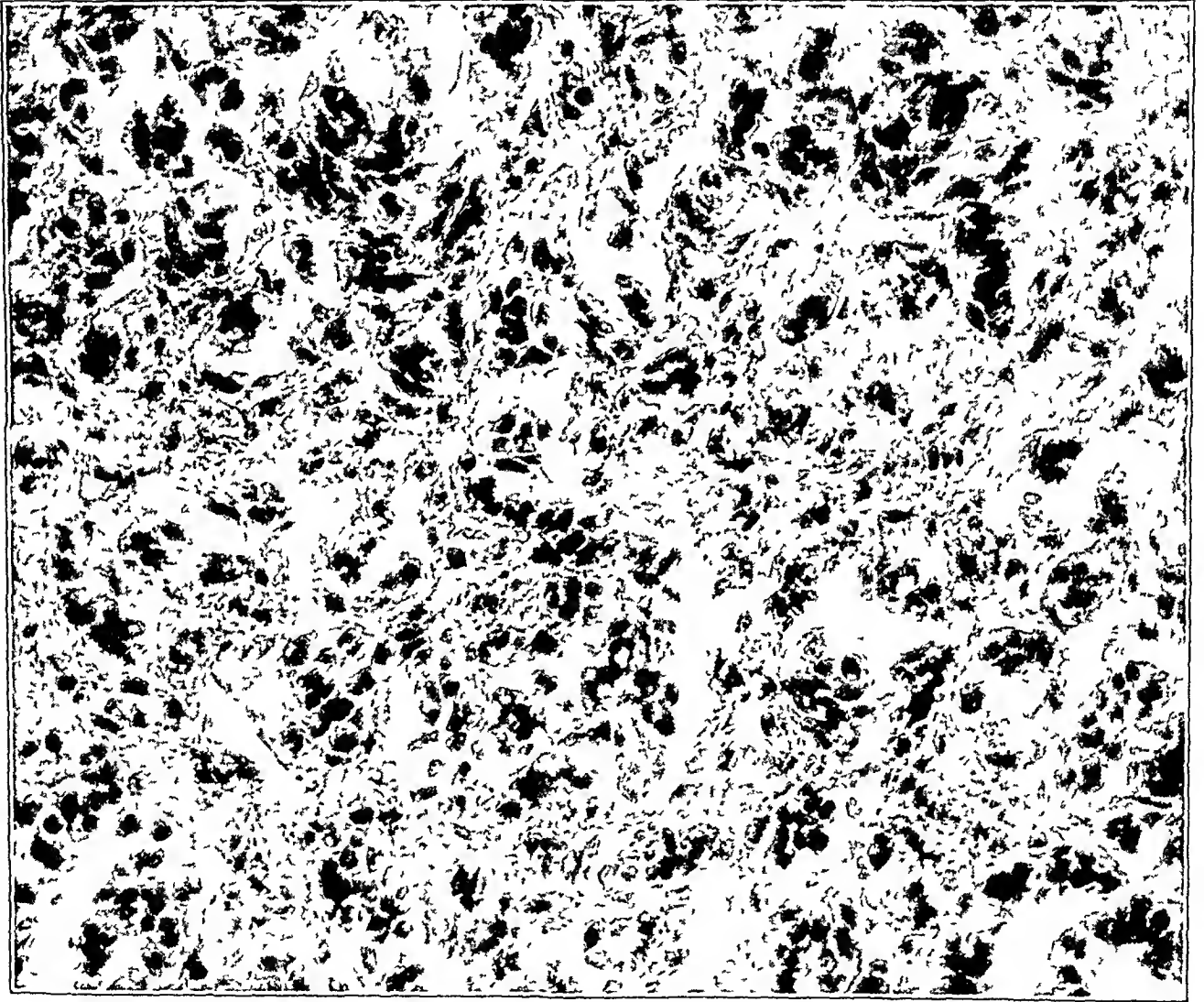


Fig 1—Section through a tumor showing the medullary character, large cells with ample cytoplasm and highly cellular structure

The patient's pain could not be relieved, on May 10 he began to fail rapidly and was kept under sedation with large doses of morphine, he died on May 18, 1944.

Histologic Study—The section of the conjunctival tumor and that of the preauricular lymph node showed the same medullary tumor tissue, consisting of large cells with ample cytoplasm and highly polymorphous nuclei. The cells were uniform in shape and size. Round and oval vesicular nuclei alternated, the chromatin was fine and widely dispersed. Some of the cells were exceedingly

large and resembled somewhat the giant cells of Hodgkin's disease. This resemblance is not surprising in view of the origin of both cells from the reticulum cells. Few mitotic figures were discernible, vascularity was rich. The cytoplasm of the smaller cells was variable in quantity and occasionally showed pseudopods, indicating ameboid activity. The origin of the cells was substantiated by the silver impregnation, which revealed close contact between the cells and the argentaftin fibrils. These fibrils not only surrounded large cell groups with a

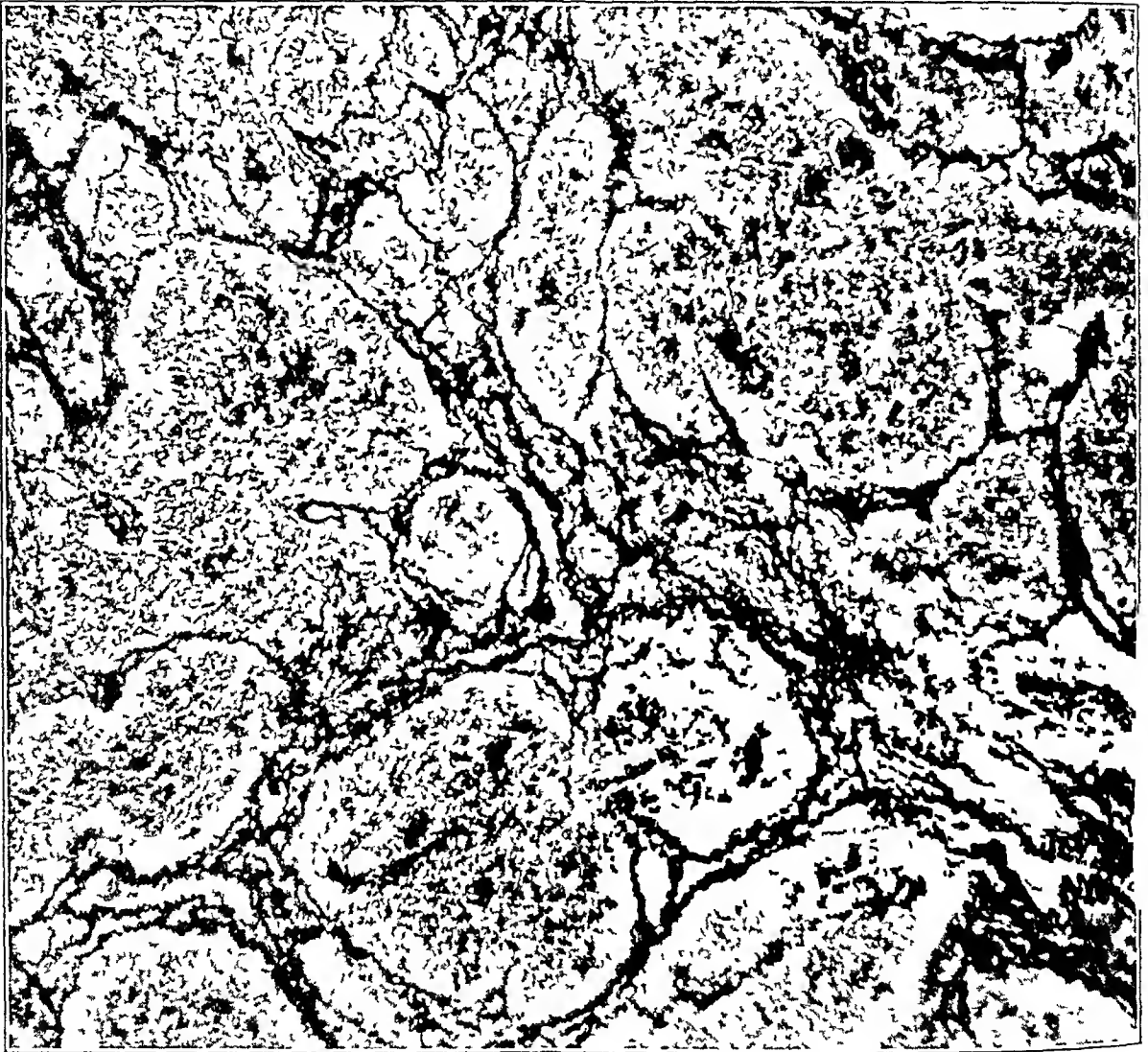


Fig 2—Section from the same specimen with silver staining, exhibiting the rich texture of argentaftin fibers, the characteristic feature of reticulum sarcomas
× 465

ringlike structure but permeated the cell groups coming into close contact with the individual cells.

A similar relation between the parenchyma of the tumor and the reticulum is the property only of tumors arising from the fibril-producing elements. In other tumors, particularly carcinomas, the argentaftin fibrils remain outside the

parenchyma or penetrate the latter only where strands of connective tissue on blood vessels carry reticulum cells along. No such fibrils enter between the individual cells. In this case the strands formed a network, constituting the stroma. The highly cellular character of the tissue and its great polymorphism are indicative of the malignant tendency.

The unilateral growth, which originated in the upper and the lower palpebral conjunctiva, appeared as extremely large papillary hypertrophies and were of firm consistency. The preauricular node and the lymph nodes of the neck were enlarged and palpable. About five months later the patient experienced unbearable pain in the back, had a septic temperature with a sterile blood culture and died about seven months after the tumor appeared on the conjunctiva, with symptoms suggestive of multilocular metastases in the spine.

COMMENT

The ophthalmologic literature reveals 2 cases of a conjunctival tumor diagnosed as reticulum cell sarcoma. But in both cases the tumor was local, without the systemic involvement characteristic of reticulum cell sarcoma. The first case, reported by Siotto,²⁶ was that of a girl aged 17 years. The red cell count was 4,500,000, the hemoglobin concentration 70 per cent and the white cell count 6,500 with 65 per cent neutrophils, 1 per cent eosinophils, 32 per cent lymphocytes and 20 per cent monocytes. There was enlargement only of the submandibular lymph node, and the patient was free of symptoms after removal of the growth and irradiation and remained so at the time of examination, six months later. The second case, reported by Black,²⁷ was that of a man aged 67, in which a dark, plum-colored tumor of primary type was attached by fibrous trabeculae to the external rectus muscle. The bulk of the tumor consisted of large, closely packed cells, with round or oval vesicular nuclei and ill defined cytoplasm, and the characteristic reticulum cells. However, staining for reticulum was not reported on, and generalized symptoms were missing, as they were in the case of Siotto. The lack of such generalized manifestations in both cases leaves the classification of the tumor as a reticulum cell sarcoma a moot question, to say the least. The reticulum cell sarcoma may occur at all sites of physiologic location of lymphoid tissue and does not spread by metastasis from the site of the first clinical manifestation but, rather, spreads by systemic involvement of the entire system, which was so evident in our case that it eliminated the element of doubt and the need of further investigation.

The sarcomas consisting of reticulum cells are tumors of rapid growth and of highly invasive type, localized occasionally in the begin-

26 Siotto, G. Contributo alla conoscenza del reticuloma della congiuntiva (osservazione clinico-istologica), *Rassegna ital. d'ottal.* 9:477, 1940.

27 Black, G. Reticulum Cell Sarcoma, *Tr. Ophth. Soc. U. Kingdom* 62:316, 1943.

ning but spreading locally and along the lymph vessels and often setting up distant, blood-borne, metastases. The most usual sites of origin are the lymph nodes, liver, bone marrow and respiratory, digestive and urogenital tract, but occasionally the growth may arise in any other organ containing lymph tissue elements. The growth represents the malignant proliferation of the cells of the reticuloendothelial system of varying degrees of maturity, with the outstanding characteristic of proliferation of the argyrophilic reticulum.

Consideration of the normal anatomic relations and the histologic structure of the conjunctiva furnishes ample proof that tumors may originate occasionally primarily in the conjunctiva. The subepithelial accumulation of lymphocytes and plasma cells is absent in the newborn, but beginning with the third month lymphocytic infiltration and small nodules are visible, especially in the upper fornix. The normal conjunctiva shows a prominent subepithelial follicle-like accumulation of small lymphoid cells in the tarsal portion, the number diminishing toward the bulbar portion of the conjunctiva. The reticuloendothelial system is well represented in the conjunctiva. I²⁸ was the first in the ophthalmologic literature to report, in 1913, on an extensive study of this system in the eye. Vital staining with lithium carmine, pyrrhol blue and trypan blue was employed, and the presence of the vitally stained cells under normal and inflammatory conditions was considered. The plasmatocytes were found in large numbers not only in the palpebral but in the bulbar part of the conjunctiva, at the latter site even a large accumulation was noted. In the subepithelial adenoid layer of the palpebral conjunctiva the plasmatocytes were mixed with the lymphoid elements. My observations were later confirmed by numerous other authors, among them Schnaudigel, Lohlein and Albrich, and the presence of these cells constitutes a generally accepted and proved histologic feature of the conjunctiva. Aschoff and Kiyono, in 1913, introduced the term histiocyte to designate the mesenchymal mononuclear phagocyte and popularized the concept of the reticuloendothelial system. The fact that the conjunctiva under normal conditions contains both lymphoid tissue and elements of the reticuloendothelial system constitutes the basis of malignant proliferation, primary tumors arising in the conjunctiva spread through this system in the same way as do the malignant growths of the same type arising in the lymph nodes.

31 Lincoln Park

28 Rados, A. Die Ausscheidung von intravenos injiziertem Carmin und Trypanblau im Auge, Arch f Ophth 85 381, 1913, Ueber die vitale Farbbarkheit der Endothelien der Descemetischen Membran, Klin Monatsbl f Augenh 17 421, 1914

AQUEOUS FIBRIN FIXATION OF CORNEAL TRANSPLANTS IN THE RABBIT

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NEW YORK

PUBLISHED reports of the use of fibrin as a substitute for sutures aroused my interest in the possibility that this material might be used in corneal grafting. The use of plasma proteins in surgery has been greatly expanded under the impetus of the recent war, particularly since the Harvard Physical Chemical Laboratories had been commissioned to study the fractionation of human blood plasma. A great many uses have been developed from the fibrinogen fraction, which is the biologic plastic cement substance of the blood.

Fibrinogen molecules are long and narrow and become oriented in parallel in a fast flowing stream¹. When a clot is formed, these molecules form a meshwork pattern. The mechanism of clotting is believed to be brought about by the action of thrombin on fibrinogen². Thrombin exists in the blood plasma as prothrombin and is transformed into thrombin in the presence of calcium ions by thromboplastins. These thromboplastins are liberated from injured tissue cells. Traces of thrombin in the blood are neutralized by antithrombins, and fibrinolytic enzymes are present in the plasma which dissolve fibrin clots after a variable period. There are also certain chemical agents which can prevent clotting, such as heparin, which is believed to inhibit the formation of thrombin from prothrombin, and hirudin, which prevents the action of thrombin on fibrinogen³.

This work was done under a grant from the Ayer Foundation.

From the Corneal Research Laboratory of the Manhattan Eye, Ear and Throat Hospital.

Read at a meeting of the New York Academy of Medicine, Section of Ophthalmology, May 21, 1945.

1 Cohn, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L., Jr., and Armstrong, S. H., Jr. The Characterization of the Protein Fractions of Human Plasma, *J. Clin. Investigation* **23** 417-432, 1944.

2 Edsall, J. T., Ferry, R. M., and Armstrong, S. H., Jr. The Proteins Concerned in the Blood Coagulation Mechanism, *J. Clin. Investigation* **23** 557-564, 1944.

3 Howell, W. H. Textbook of Physiology for Medical Students and Physicians, ed. 12, Philadelphia, W. B. Saunders Company, 1933, p. 486.

The Harvard group has processed fibrinogen into a number of forms, such as fibrin foam, films and plastics,⁴ which have been used in the solution of a great many surgical problems. This material has been used as a protective agent in the surface treatment of burns,⁵ as an aid in the operative removal of renal calculi⁶ and as a hemostatic agent in neurosurgery⁷, it has also been employed to repair dural defects,⁸ to hold skin grafts in position,⁹ to aid in reconstructive surgery¹⁰ and to cement together the severed ends of peripheral nerves¹¹.

The adhesive action of natural fibrin has also been recognized in various operations about the eye, but in order to form fibrin blood vessels must be severed. Since human aqueous contains only traces of fibrinogen¹² and since the cornea is avascular, there is no natural source for fibrinogen in corneal surgery. The aqueous that regenerates after a paracentesis on the human eye contains slightly larger amounts of fibrinogen. In animal eyes, however, the protein content is much increased after paracentesis¹³. In rabbits the regenerated aqueous contains such a large amount of fibrinogen that a clot forms within several minutes of the time the anterior chamber has been opened. This property of rabbit aqueous in relation to healing of corneal wounds was studied by Brown and Nantz¹⁴. These authors prepared corneal trans-

4 Ferry, J. D., and Morrison, P. R. Fibrin Clots, Fibrin Films and Fibrinogen Plastics, *J Clin Investigation* **23** 566-571, 1944

5 Hawn, C. Z., Bering, E. A., Jr., Bailey, O. T., and Armstrong, S. H., Jr. A Note on the Use of Fibrinogen and Thrombin in the Surface Treatment of Burns, *J Clin Investigation* **23** 580-585, 1944

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8 Bailey, O. T., and Ingraham, F. D. Fibrin Films in Neurosurgery, with Special Reference to Their Use in the Repair of Dural Defects and in the Prevention of Meningocerebral Adhesions. *J Clin Investigation* **23** 597-600, 1944

9 Cronkite, E. P., Lozner, E. L., and Deaver, J. M. Use of Thrombin and Fibrinogen in Skin Grafting, *J A M A* **124** 976-978 (April) 1944

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11 Young, J. Z., and Medawar, P. B. Fibrin Suture of Peripheral Nerves, *Lancet* **2** 126-128, 1940. Tarlov, I. M., and Benjamin, B. Plasma Clot and Silk Suture of Nerves, *Surg, Gynec & Obst* **76** 366-374, 1943

12 Hayano. Ueber die Fermente in Kammerwasser, in *Festschrift für Prof Komoto*, abstracted, *Klin Monatsbl f Augenh* **65** 755, 1920

13 Hagen, S. Weitere Untersuchungen über die Regeneration des Kammerwassers im menschlichen Auge, *Klin Monatsbl f Augenh* **66** 493-507, 1921

plants 4 to 5 mm in diameter by means of a small cataract knife. A traction suture was inserted in the center of the corneal apex before the transplant was incised. The transplant was replaced in situ after it had been detached, and fibrin was allowed to form to cement the graft in place. At various intervals the traction necessary to separate the graft from its bed was measured and after four hours was found to be 11,000 times the weight of the graft.

The problem which was studied was the use of fibrin as a complete substitute for sutures in performing corneal grafting operations in the rabbit.

METHOD

Since the operation requires about twenty minutes to perform, it was necessary to prevent the premature formation of fibrin clots. This was done by the intravenous injection of heparin. In a 2 Kg rabbit, 5 mg of heparin prevents

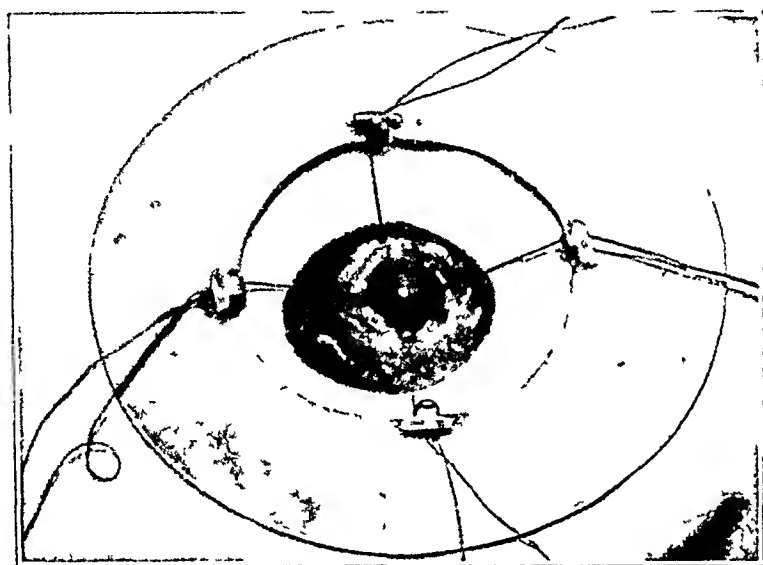


Fig 1—The sutures are passed through the superficial layers of the limbus and wound around cleats on the aluminum disk. No speculum is necessary, as the sutures hold the lids out of the way.

aqueous clotting for thirty minutes. To reverse the action of heparin, Hemostatic Globulin (Lederle) was used locally. This material is prepared from rabbit plasma and contains the thrombin fraction.¹⁴

The rabbits were given a basal anesthesia by intravenous administration of sodium pentobarbital, supplemented by the injection of 4 per cent procaine hydrochloride into the lids and behind the eyeball. The eye was fixed by four sutures passed through the limbus and tied to an aluminum disk provided with cleats. A central suture was placed in the cornea and a 4.5 mm disk removed with trephine and scissors. The disk was replaced temporarily while a graft was removed with

14 Brown, A. L., and Nantz, F. A. Corneal Healing. The Adhesive Power of Aqueous Fibrin in the Rabbit, Preliminary Report, *Am J Ophth* **27** 1220-1224, 1944.

15 Parfentjev, I. A. A Globulin-Fraction in Rabbit's Plasma Possessing a Strong Clotting Quality, *Am J M Sc* **202** 578-584, 1941.

the same trephine from a donor rabbit's eye. Then the excised disk was lifted from the recipient eye, 1 minim (0.065 Gm.) of Hemostatic Globulin dropped into the anterior chamber and the graft placed in situ. Another minim of the globulin was placed on top of the graft, a drop of a 3 per cent solution of atropine sulfate was instilled, and the lids were sutured with three intramarginal sutures.

For the first five postoperative days the rabbit was left untouched. Then the lid sutures were removed, and atropine was instilled daily.

COMMENT

Large amounts of fibrin begin to form as soon as the globulin is introduced, and the transplant must be placed in its bed promptly and with care so that its position does not have to be shifted. A layer of fibrin also forms on top of the cornea, precipitated from the released aqueous. With a well fitted graft, the anterior chamber will fill rapidly and reform under observation. At the time the lid sutures are removed



Fig 2—A clear graft three weeks after operation.

the graft is usually hazy, as a result of interstitial edema. This haziness requires one to two weeks to clear.

The use of rabbits for this experiment has imposed several obstacles which do not exist with the human subject. The exposed position of the rabbit eye and our inability to maintain immobilization of the animal during the postoperative course have predisposed to accidents which are avoided in the human subject. Also, the operation is technically more difficult in the rabbit because of the softer consistency of the cornea. Several authors have reported the performance of the grafting operation in human eyes without the use of sutures, but with indifferent success.¹⁶ To apply the fibrin fixation method to human subjects, both fibrinogen solution and thrombin would have to be added.

¹⁶ Gradle, H. S. The Present Status of Keratoplasty, *Am J Ophth* 4:895-899, 1921. Thomas, J. W. Transplantation of Cornea, *Tr Ophth Soc U Kingdom* 50:127-141, 1930.

RESULTS

This procedure was applied to corneal transplantation in 37 rabbits. In 32 of these animals the graft held and healed in position. In 5 rabbits the graft slipped, in 1 of these there was gross infection. The transplants remained clear for periods up to six months in 18 rabbits and became opaque in 14 rabbits.

SUMMARY AND CONCLUSION

Corneal grafts were performed in rabbits, using the fibrin formed in the anterior chamber as the only fixing agent. The technic used is described, and the procedure was performed in 37 eyes. The grafts held in 86 per cent and remained clear in 48 per cent of the eyes. We hope soon to be able to use fibrin in a similar manner in operations on the human eye.

We believe that there is great significance in the successful use of fibrin to hold corneal grafts in place during healing. The significance is great not only because the operation itself may be vastly simplified thereby but because the corneal graft is an ideal test medium for wound healing of all types. The area of contact between graft and host, after the anterior chamber has reformed, is of very small dimensions. Also, the tissue reaction to the fixing agent is immediately apparent in the transparency of the corneal graft.

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DISCUSSION

DR R. TOWNLEY PATON, New York. Dr. Katzin has demonstrated that the aqueous fibrin fixation of corneal transplants is possible in rabbits. A similar method has been applied to the human eye in 1 case. It was not deemed safe to eliminate the sutures to hold the transplant in place. It was noted, however, that the anterior chamber refilled immediately as the fibrin was dropped on the cornea. Also, it seems that the fibrin acts somewhat as a protective dressing. I hardly think that in operations on the human eye sutures will be entirely eliminated, but the application of fibrin will act as a reinforcement to keep the graft in place, and the fibrin, when injected into the anterior chamber, will act as a cushion and a protection to the lens.

DR RAMON CASTROVIEJO, New York. One will have to wait until a method of applying fibrin to hold corneal transplants in place has been used extensively in order to be able to state whether such a method will be of practical value. From the experience gained in cataract surgery, it may be assumed that holding the transplant in the cornea of the host will have to be accomplished by the same methods as those used for closing the incision in cataract extractions. In cataract extrac-

tions the incision was first left to cicatrize without sutures, then, to prevent prolapse of the iris and other postoperative complications, conjunctival sutures were used, and recently corneoscleral sutures, which close the incision more firmly, are favored by many ophthalmic surgeons

I believe it will be found that the best suture is that which will keep the graft in the eye of the host more securely in place, without danger of prolapse

Dr R Townley Paton gave help and guidance and Miss Florence Schorske and Mrs Fannie Gruber technical assistance in this work

Clinical Notes

CONJUNCTIVITIS AND DERMATITIS DUE TO "BEACH APPLE"

Report of Thirteen Cases

CAPTAIN PHILIP C GRANA, MEDICAL CORPS, ARMY OF THE UNITED STATES

IN 1942, in Panama 13 cases of acute conjunctivitis and dermatitis were observed and attributed to an agent which, so far as could be determined had not previously been reported in a large number of cases.

During maneuvers of an infantry regiment one company took up defensive positions along a stretch of Pacific Ocean beach at night. The men dug foxholes and then proceeded to camouflage them by utilizing pieces of shrub found in the vicinity. This is in accordance with good military practice, as it affords a disguise which conforms with the surrounding terrain. It so happened that "beach apple" plant was easily accessible, and hence it was used.

The scientific name of the plant is *Hippomane mancinella* L. (Euphorbiaceae). The common names in current use are "manzanillo" and "beach apple." It is described as a gray-barked, round-topped tree found on the seabeaches of the West Indies and Central America. The small green fruit resembles a crab apple and, if eaten, sometimes causes death¹.

Not more than two hours after the men dug in on the beaches, 3 casualties were brought to the clearing station. The history was essentially the same in all 3 cases, the men had used "beach apple" for camouflage and had inadvertently touched their eyes. The chief complaints consisted of excruciating pain referable to the orbital contents, intense photophobia, blurring of vision and profuse lachrimation.

Examination revealed pronounced swelling of the lids, associated with redness. The palpebral and bulbar conjunctivas were intensely injected in a diffuse fashion, and there was some slight evidence of chemosis. Tearing was pronounced. A more detailed study of the eyes could not be performed, owing to inadequate facilities. Furthermore, the patients resisted prolonged exposure of the eye for examination because of the intense pain and photophobia.

In addition to the eye, the skin of the face showed a diffuse, patchy erythema and swelling. Subsequently, 10 additional casualties arrived in a group at the clearing station. The history was the same as that previously elicited except that several of the soldiers denied any direct contact with "beach apple", yet the lesions observed were similar to those of the men who had touched the plant. They did state, however, that they were in the vicinity of the plants but were engrossed in duties other than camouflage of foxholes. In this group, dermatitis varied in severity from erythema with mild swelling to large vesicles and more widespread redness. One man had camouflaged his foxhole and had

1 Allen, P. H. Poisonous and Injurious Plants of Panama, *Am J Trop. Med (supp)* 23 3-76 (Jan) 1943

then proceeded to remove ticks from his genitals. The result was a marked swelling of the glans and the shaft of the penis.

The history and clinical appearance indicated a contact reaction of the eyes and skin to some noxious agent in the plants. Spread from one part of the body to another was thought to be caused by contaminated hands.

Since ocular pain was the most distressing symptom, treatment had to be directed toward its relief. Despite administration of 1 grain (13 mg) morphine sulfate to each patient prior to arrival at the clearing station, no substantial analgesic effect was obtained. It was then reasoned that local dilution of the toxic substance was necessary. A lukewarm dilute solution of boric acid was used as an eyewash. Its application was repeated many times. Care was taken to catch the fluid escaping from the conjunctival sac. A piece of cotton pressed against the cheek was used for this purpose. Then, with the eyes closed, the external surface of the lids was washed with the same solution. The skin involved elsewhere on the body was bathed with copious quantities of dilute solution of sodium bicarbonate. The effect of this simple treatment was dramatic. Relief of pain was immediate and complete.

No particular rationale is offered for the use of solution of sodium bicarbonate except for its cleansing action. Solution of boric acid was used, first, for its mechanical cleansing action, second, for its diluent effect on the toxic agent, and third, for its recognized soothing effect as a constituent of the usually prescribed eyewash.

All casualties were evacuated to a nearby station hospital. It was later learned that the average stay in the hospital was three days. Treatment used in the clearing station was recorded on the individual medical field tag and was continued in the hospital in similar fashion. No complications occurred. The objective signs disappeared almost entirely during the short period of hospitalization.

The importance of preventive treatment is indicated by the immobilization of 13 men from a single company of infantry in two hours. It is conceivable that a larger number of soldiers could be made non-effective, an eventuality which might result in failure to accomplish their mission. This danger can be averted by familiarization of all ranks with the consequence of contact with local flora, such as "beach apple."

SUMMARY

Thirteen cases of conjunctivitis and dermatitis caused by a toxic plant are reported.

Pain was the most prominent symptom, and treatment was directed toward its alleviation. The intensity of the reaction and the short interval of time required to produce it were worthy of note.

The use of dilute solution of boric acid for the eyes and dilute solution of sodium bicarbonate for the skin was found effective.

The average stay in the hospital was three days, and no complications occurred.

Preventive measures are stressed. Troops serving in areas infested with this plant should be warned of its harmful effects.

Ophthalmologic Reviews

EDITED BY DR FRANCIS HEED ADLER

ALKALI BURNS OF THE EYE

I Review of the Literature and Summary of Present Knowledge

WILLIAM F HUGHES Jr, MD

BALTIMORE

THE serious nature of alkali burns of the eye was first emphasized in 1813 by George Beer, who stated

extensive and intensive chemical injuries of the eye are produced by slaked and unslaked lime often acting so destructively that the entire cornea is disintegrated and suddenly changed into a greyish pulp which can be washed away from the iris below with a brush. The effect of the mineral acids, if they are also as saturated, is rarely so destructive for the cornea as is unslaked lime.

Since then these burns have been the subject of intensive study, and a number of papers have appeared on the pathologic and the chemical changes produced in the corneal stroma by alkalis. In regard to treatment there are two sharply conflicting schools of thought, one school advocating conservative treatment with irrigations, neutralizing agents, symptomatic therapy and, later, corrective surgical measures when indicated, while the second school urges the immediate removal of all necrotized conjunctiva and replacement with a mucous membrane graft.

The purpose of this review is to summarize the present state of knowledge on this subject and to attempt an evaluation of the various investigations and treatments thus far reported. This is preliminary to reports of additional studies pursued at the Wilmer Ophthalmological Institute. The subject will be discussed under the following headings:

1 *Clinical and pathologic course of alkali burns of the eye*

2 *Factors governing the severity of the lesion*

- (a) Character of the cation
- (b) Concentration of the alkali
- (c) Duration of the exposure
- (d) pH of the solution
- (e) Speed of penetration

3 *Mechanism of Action*

- (a) Production of heat

The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital.

- (b) Withdrawal of water
- (c) Effect on corneal constituents
 - Collagen
 - Mucoid
 - Albumin
 - Inorganic salts
 - Stroma cells
- (d) Toxic hydrolysates
- (e) Necrosis of limbal vessels

4 Treatment

- (a) Emergency measures—experimental results
- (b) Later treatment—general principles
- (c) Comparison of clinical results conservative treatment versus Denig graft

CLINICAL AND PATHOLOGIC COURSE OF ALKALI BURNS

The outstanding papers dealing with the clinical and pathologic course of alkali burns are those of de Gouvea (1869), Guillery (1906), Wagenmann (review in 1911), Siegrist (1920) and Yoshimoto (1928). All these authors have agreed that the ultimate prognosis cannot always be estimated at an early examination, since in many cases of apparently mild burns late infiltrations, necrosis or ulceration of the cornea develops. Some of the factors which govern the severity of the lesion are discussed later. From a review of the literature and from studies at the Wilmer Institute, which will be reported in detail later, the most prominent characteristics of a severe alkali burn can be summarized in chronologic order, as follows:

Time	Characteristics
1-10 min	Rapid penetration of alkali through cornea into anterior chamber, diminished tactile sensitivity of cornea, disintegration and sloughing of conjunctival and corneal epithelium, opalescent opacification of cornea, washed-out appearance of substantia propria with beginning disintegration of stromal cells, fragmentation of corneal endothelium, hyperemia of iris
2 hr	Edema and ischemia of conjunctiva and limbal (corneoscleral) region of the eyeball, infiltration of polymorphonuclear cells into conjunctiva, episcleral tissues and periphery of cornea, corneal edema, giving rise to opalescent haziness of cornea, with wrinkling of Descemet's membrane ("striate keratitis"), exudation of serum into anterior chamber, Greef blebs and edema of ciliary processes
18 hr	Beginning regeneration of corneal epithelium, marked corneal edema, loss of metachromatic staining of corneal mucoid, disappearance of stromal cells, increase of purulent infiltration into conjunctiva, cornea and anterior chamber, opacity of anterior capsular and subcapsular region of lens

24-48 hr	Moderate mucopurulent discharge in cul-de-sac, intensification of opacification, edema and purulent infiltration of cornea, appearance of spindle-shaped cells at periphery of lesion, regeneration of corneal endothelium
3-6 days	Petechial hemorrhages in ischemic areas of conjunctiva, varying amounts of superficial corneal ulceration, without apparent progression of corneal infiltration or opacification, persistence of iritis
7-13 days	Stage of gradual recovery or progression of corneal opacification and ulceration, varying amounts of mucopurulent discharge from eye, formation of adhesions between severely burned portions of bulbar and palpebral conjunctivas, localized corneal infiltrates of polymorphonuclear and mononuclear cells, with ulceration over such areas, beginning vascularization of cornea from limbal vessels, superficial loops from unthrombosed conjunctival vessels or brush-like projections from deep scleral plexus in ischemic regions, continued proliferation of spindle-shaped cells in cornea, subsidence of corneal edema, improvement of iritis
14 days and over	Abatement or progression of symptoms previously described, great resistance of Descemet's membrane to perforation, healing of corneal ulceration by proliferation of opaque fibrous tissue and blood vessels Complications of severe burns Symblepharon with overgrowth of cornea by a vascularized membrane, persistent, progressive or recurrent corneal ulceration, occasionally leading to perforation, permanent corneal opacification, staphyloma of cornea, persistent or exudative iritis, at times ending in phthisis bulbi, secondary glaucoma or cataract

FACTORS GOVERNING SEVERITY OF LESION

The severity of alkali burns depends slightly on the character of the cation but more on the concentration of the alkali, the duration of exposure, the *pH* of the solution and its penetrability. These factors will now be discussed.

Character of the Cation—The severity of the lesion in alkali burns is not greatly influenced by the type of cation. After exposure to ammonia the damaged cornea initially appears opalescent. In contrast, sodium hydroxide, potassium hydroxide and, especially, calcium hydroxide may produce a porcelain white opacification of the cornea immediately after exposure (Guillery, 1906). The ultimate prognosis for ammonia burns, however, is at least as poor as is that for lye and lime (calcium oxide) burns. Vinogorov and Kopit (1936) found that, although sodium hydroxide and potassium hydroxide produced similar lesions, the latter were somewhat more severe. A comparison of the ocular reactions to various alkaline calcium derivatives by Leonardi (1927) revealed differences in rapidity of development and in intensity but not in type. He produced a "scab-like" opacification of the cornea with the following substances in the

exposure time indicated calcium oxide, two minutes, calcium oxide with dye and fish glue, ten minutes, calcium silicate and cement, twenty minutes, mortar and argillaceous limestone, one hour

In view of the repeated attempts of various investigators and clinicians to extract calcium from lime-burned corneas with the use of ammonium salts, it is interesting to note that 0.1 cc of a neutral and isotonic solution of calcium chloride (1.7 per cent) can be injected intracorneally without damage to the tissue. In his review, Cramer (1930) stated that a 30 to 50 per cent solution of calcium chloride can be safely instilled into the eye. Pichler (1924) reported a case in which solid particles of a calcium chloride powder (containing 90 per cent calcium chloride, 2 per cent potassium chloride, 3 per cent calcium oxide and 5 per cent unknown materials) were blown into the eyes of a man. The particles embedded in the cornea were rubbed off, and the cornea healed promptly. There is little direct evidence that combinations of calcium with organic material or inorganic salts in the cornea are the cause of the poor prognosis or the permanent corneal opacification following lime burns (see later sections). It is much more likely that the main destructive action of lime is caused by the alkalinity, or high pH , of the calcium hydroxide solution. The relative unimportance of the cation in alkali burns is in sharp contrast to the importance of the anion in acid burns (Friedenwald, Hughes and Herimann, 1944).

Concentration of the Alkali—It is difficult to estimate by a study of case histories the minimal concentration of various alkalis which will produce damage to the human eye, because the exact concentrations are usually unknown, the concentrations of the solutions are ordinarily far above the minimal tolerance of the eye and the exact degree of contact with the eye cannot be ascertained. Guillery (1906) produced opacities of the rabbit cornea within a few minutes by brushing on 5 per cent sodium hydroxide, 10 per cent potassium hydroxide or 25 per cent calcium hydroxide. These solutions, as well as 10 per cent ammonia (ordinary household strength), have been used by many investigators to produce standard devastating lesions for treatment experiments. Yoshimoto (1928) found that a few drops of fifth-normal (0.8 per cent) sodium hydroxide produced a transient opacity for three days, whereas the instillation of half-normal (2.0 per cent) sodium hydroxide resulted in perforation of the cornea in seven days. For ammonium hydroxide, he found that a normal (3.5 per cent) solution produced a transient corneal opacity for three days, a twice normal (7 per cent) solution gave rise to an opacity lasting fourteen days, with only slight residual clouding, and a three times normal (10 per cent) solution produced a corneal ulcer with hypopyon which healed in eighteen days, leaving a dense corneal leukoma.

Duration of Exposure—Much of the experimental work can be criticized from a quantitative standpoint, in that the instillation of only a few drops may be followed by reflex lacrimation, the tears diluting the alkali and washing it out of the eye. Clinically, the importance of the duration of exposure and the concentration of the alkali is emphasized by the ill effects which follow retention of solid particles of lye or lime hidden within the conjunctival folds of the eye. Unless such particles are completely removed the corneal opacification becomes progressively worse.

p_H of the Solution—In experiments to determine the p_H tolerance of the cornea, Friedenwald, Hughes and Herrmann (1944) irrigated the eyes of rabbits for ten minutes and made intracorneal injections of a buffer solution of known and well established alkaline p_H. At higher p_H levels, dilutions of sodium hydroxide were used. These authors found that a p_H over 11.5, or 0.005 N (0.02 per cent) sodium hydroxide, would damage both the intact cornea and the corneal stroma.

Speed of Penetration—Pichler (1910) instilled several drops of 10 per cent aqueous ammonia into the conjunctival sac of a rabbit. Ten minutes later the eye was enucleated and washed until no ammonia could be demonstrated in the wash water, and the aqueous withdrawn with a syringe was found to give a strong reaction for ammonia with Nessler's reagent. Ammonia could still be demonstrated in the aqueous after two hours but was absent at five hours. Siegrist (1920) obtained a doubtful positive reaction of the aqueous with Nessler's reagent five seconds after the instillation of strong solution of ammonia, a distinct positive reaction after fifteen seconds and a strong positive reaction after thirty seconds. Berezinskaja (1937) found that sodium hydroxide penetrated into the anterior chamber within five minutes after the instillation of a 5 per cent solution into the conjunctival sac of rabbits. De Gouvea (1869) demonstrated the presence of calcium chemically in the anterior chamber within twelve hours after exposure to lime.

MECHANISM OF ACTION OF ALKALI BURNS

Much speculation and experimental work have centered on a search for the causes of late infiltrations and ulceration of benign-looking alkali burns and the progressive nature of more severe burns.

Production of Heat—The evolution of heat from dissolving calcium oxide or concentrated alkali solutions in water or tears has been considered a possible source of additional damage to the ocular tissue. Andreae (1899) found that it required ten to fifteen minutes before the slaking process of solid lime in the eye would produce a temperature over that of the blood. Lacrimation would tend to dilute the lime and lower the temperature. After the instillation of calcium oxide

into the conjunctival sacs of rabbits, measurement of the temperature by thermoelectric methods show no rise over 42 C with the lids open or over 45 C with the lids closed (Rosenthal, 1902) The temperature of the normal conjunctival sac of the rabbit has been reported by von Michel to be 32 C Such a small increase in temperature could not damage the ocular tissues Application of a thermophore at 45 C is tolerated by the human cornea

Withdrawal of Water—Concentrated alkaline solutions, especially ammonia, have a strong affinity for water It has been stated repeatedly in the literature that this property results in a withdrawal of essential water from the tissues However, no experimental evidence can be found to support this hypothesis

Effect of Alkali Burns on Chemical Constituents of the Cornea—Alterations in the chemical constituents of the cornea following exposure to alkali have been investigated in some detail by Rosenthal (1902), Pagenstecher (1905), zur Nedden (1906), Guillery (1906), Haurowitz and Braun (1922) and Braun and Haurowitz (1923) Since the epithelium and endothelium make up only about one ninth of the weight of the cornea, the chemical analyses have largely represented changes in the corneal stroma Kjause (1934) tabulated the values for the chemical composition of the normal beef cornea which may be summarized as follows

Constituents of Beef Cornea	Percentage by Weight
Water	81.1
Inorganic matter (ash)	0.2
Organic matter	18.7
Water-insoluble proteins	18.4
Collagen	15.1
Mucoid	3.0
Elastin	Trace
Water-soluble proteins (albumin and globulin)	0.15
Extractives (water soluble, e. g., sugar)	0.13
Lipids (ether soluble)	0.04

Corneal Collagen Since collagen comprises about 80 per cent of the organic material of the cornea, it has been hypothesized by Pagenstecher (1905) that the corneal opacity in cases of lime burns is due to a calcium-collagen combination

Haurowitz and Braun (1922), following the technic of Morner, extracted all the mucoid from beef corneas with tenth-normal ammonia The resulting preparation consisted almost entirely of corneal collagen and was proved to be free of reducing sugars by testing with Fehling's solution after hydrolysis Treatment of this preparation with lime resulted in some absorption of calcium, demonstrable chemically These

corneas, devoid of mucoid but containing collagen, lost their swelling capacity after treatment with lime but did not show any reduction in translucency (the latter being also demonstrated by Morner) Zur Nedden (1906) found that the addition of lime water to various commercial collagens produced no opacification Haurowitz and Braun (1922) noted that alcohol-precipitated gelatin was dissolved by sodium hydroxide but not by ammonia or lime

Corneal Mucoid Mucoid (hyaluronosulfuric acid, or mucopolysaccharide) comprises about 20 per cent of the organic material of the corneal stroma According to Levene (1925), Meyer and Chaffee (1940) and others, the composition of the complex polysaccharide associated with the protein probably contains a relative proportion of 1 molecule of acetylhexosaminesulfuric acid and 1 molecule of glycuronic acid As previously noted, this corneal mucoid can be extracted completely with tenth-normal ammonia (Morner) and other alkaline solutions Guillery (1906) found that supersaturated solutions of calcium hydroxide and calcium chloride precipitated mucoid Haurowitz and Braun (1922) also found that ammonia extracts of corneal mucoid became somewhat cloudy after the addition of either lime water or sodium chloride, being cleared subsequently by the addition of hydrochloric acid Mucoid was also absorbed on the particles of a lime emulsion They mentioned the fact that the behavior of proteins is dependent on many quantitative factors, e.g., concentration, temperature, salt content, p_H and other physical-chemical factors Therefore, it would be unwise to suppose that these *in vitro* phenomena are directly applicable to the *in vivo* behavior of mucoproteins These authors (1922 and 1923) also extracted mucoid from beef corneas with tenth-normal ammonia, the remaining material showing neither traces of reducing sugars nor metachromatic staining of mucoid with mucicarmine (Mayer's carmine—ammonium hydroxide stain) or thionin However, in lime-burned corneas which were subsequently subjected to extraction with ammonia, the Fehling reaction for reducing sugars remained positive and the metachromatic staining was retained With ordinary fixation in solution of formaldehyde USP or alcohol, metachromatic staining was lost in normal corneas but not in lime-burned corneas The authors concluded that lime alters a portion of the corneal mucoid, making it no longer extractable with ammonia

Recently, estimations of mucoid in rabbit corneas damaged by various chemical agents have been made by (1) metachromatic staining with toluidine blue and (2) microchemical determinations of hexosamine by Meyer and Chaffee¹ on similarly treated corneas

¹ A detailed report of these examinations will be published separately by Dr Karl Meyer and Miss Eleanor Chaffee¹

In table 1 is shown a marked loss of hexosamine twenty-four hours after ten minutes' irrigation with twentieth-normal sodium hydroxide, whereas equally opaque corneas resulting from ten minutes' ^{2b} irrigation with half-normal hydrochloric acid showed no appreciable loss of hexosamine. There was also a distinctly greater loss of metachromatic staining of the mucoid in corneas burned with sodium hydroxide when examined at the end of twenty-four hours. In these studies, it was found that many other necrotizing substances produced some loss of corneal mucoid. Since the loss does not occur immediately,

TABLE 1—*Effect on Corneal Mucoid of Various Chemical Agents**

Substance	Time	Percentage of Opacity	Percentage of Hexosamine	Loss of Metachromatic Staining
Normal cornea		0	1.31 †	—
Sodium hydroxide (N/20)	0	81	1.27	±
	45 min	88	0.79	1
	2 hr	88	1.30	2
	4 hr	88	0.96	1
	8 hr	94	0.96	2
	21 hr	88	0.48 †	3
(Specimen dried)	2 days	81	0.37	
	2 days	92	0.19	
	1 days	88	0.31	
	6 days	90	0.28	4
Hydrochloric acid (N/2)	1 hr	66	1.23	0
	13-hr	84	1.17	0
	24 hr	92	1.20	0
(Dried)	21 hr	81	1.03	
	2 days	100	1.22	
	1 days	88	1.21	
	6 days	90	1.11	3
(Dried)	6 days	92	1.01	
Toluidine blue (0.5%)	24 hr	75	1.34	
	6 days	81	1.07 (partial)	1
Turpentine (nonspecific inflammation)	2 days	58	1.01	2
Mechanical edema (produced by damage to endothelium)	2 days	66	0.91	2 (?)

* The determinations of hexosamine were performed by Dr Karl Meyer and Miss Eleanor Chaffee and will be reported on in detail by them elsewhere.

† Standard deviation = 0.15

it may be related to secondary influences, e.g., corneal edema, damage to possible sources of hexosamine synthesis, inflammatory cells or proliferation of fibrous tissue.

In summary, there appears to be an early loss of corneal mucoid following sodium hydroxide and ammonia burns, contrasting sharply with the absence of an appreciable loss with acid burns. Haurowitz and Braun reported that exposure to lime results in an alteration of a portion of the corneal mucoid which prevents its extraction with ammonia and alcohol but does not interfere with its metachromatic staining with mucicarmine or thionin.

Albumin Since there is only a trace of water-soluble proteins (albumin and globulin) in the cornea, it would be unlikely that an alteration in these constituents could account for much of the corneal lesion. Andreae (1899) obtained a precipitate on adding lime to hen egg albumin. However, zur Nedden (1906) and Guillery (1906) prepared a heavy suspension of albumin from egg and serum, taking precautions to exclude contamination with carbonate, and found that the addition of lime water or "lime brew" produced no cloudiness or precipitation.

Corneal Elastin Kriase (1934) found a small amount of elastin in beef cornea. With respect to a possible alteration in this component, Pagenstecher (1905) observed that the fibrillae of the cornea became straight after calcium burns (instead of being wavy), apparently having lost their ability to contract.

Lipids The possibility that alkalis might saponify the trace of lipidal substances in the cornea was suggested by Leonardi (1927). There is apparently no experimental support of this hypothesis.

Formation of Insoluble Carbonates The relatively dense corneal opacity following lime burns has been considered to be due, in part at least, to the deposition of calcium carbonate crystals. De Gouvea (1869) found that the addition of acid to lime-burned corneas gave an evolution of gas bubbles, presumably from the reaction of acid and calcium carbonate. Zur Nedden (1906) also obtained gas bubbles from the addition of hydrochloric acid to slices of fresh lime-burned corneas, and Guillery (1906) confirmed this, taking care to use carbonate-free lime in burning the corneas. Zur Nedden immersed beef corneas denuded of epithelium in distilled water for three days, after which they appeared opalescent and swollen but contained no dense opacity. Addition of lime water to these corneas did not produce any dense opacification, the soluble carbonates normally in the cornea apparently having diffused out. In corneas immersed in a 0.15 per cent solution of sodium bicarbonate for three days dense white opacification developed after treatment with lime water. Control corneas immersed in distilled water for three days and treated with heavy metals (lead, silver, copper, zinc or mercury) become opaque, the mechanism of opacification apparently being different from that with alkaline calcium solutions. The normal cornea contains only traces of inorganic salts: 0.2 per cent sodium carbonate, 0.8 per cent sodium chloride and 0.03 per cent phosphate and sulfate together. Because of these minute quantities, Pagenstecher (1905), zur Nedden (1906) and Guillery (1906) stated that calcium carbonate is probably deposited secondarily, the calcium being derived from calcium-protein combinations and the carbonate from the air and tissues. Wolf (1926) stated that he saw small white particles in the corneas of 2 patients with lime burns which

he considered to be deposits of calcium salts and which slowly disappeared within a few weeks

Haurowitz and Braun (1922) found that with beef eyes denuded of epithelium an opacity was produced by the addition of alkaline solutions of calcium, barium and strontium salts but not of alkaline solutions of magnesium oxide and other alkalis or of neutral solutions of the alkaline earth salts. These investigators could demonstrate no gas bubbles on addition of hydrochloric acid to the burned corneas whether in fresh specimens, in corneas fixed with solution of formaldehyde U S P or in corneas from which the mucoid had previously been extracted. However, lime-burned corneas fixed in alcohol gave a positive reaction to the bubble test with hydrochloric acid, indicating that the calcium carbonate was formed during the process of fixation in alcohol. They found that lime-burned rabbit corneas showed an immediate rise in calcium content to twice normal values but that the calcium disappeared from the burned corneas four weeks later, although the opacity remained. This was taken to indicate that the calcium ion was not directly responsible for the corneal opacification. This evidence does not rule out the possibility that the persistent corneal opacity might be due to fibrous tissue repair, even though the earlier opacity was related to the calcium ion. These authors could detect no precipitated phosphate after lime burns with use of the molybdenum reagent.

In conclusion, although it is possible that calcium ions in an alkaline medium might increase the early opacification of the cornea by precipitation with inorganic carbonates, it is unlikely that calcium ions per se accelerate the progress of the ocular lesion or contribute much to the intensity of the final corneal opacity.

Cellular Constituents In addition to the changes in the extracellular collagenous material of the corneal stroma already outlined, consideration must also be given to the reaction of alkali with cellular constituents. One of the prominent features of alkali burns is the early disappearance of the stroma cells. What remains is completely devitalized tissue. It is possible, however, for new cells to grow into devitalized but otherwise uninjured corneal stroma. This may be seen in the reports of successful grafting of formaldehyde-fixed cornea. Burns with solid carbon dioxide result in temporary complete loss of all cellular structures in the affected area, with subsequent regrowth of new stroma cells and ultimate complete restitution of the normal histologic and clinical appearance of the cornea. It follows that the scarring, ulceration and other late changes which occur after alkali burns cannot be attributed solely to the initial destruction of cellular elements, but that some accompanying change in the collagenous or intercellular structure makes full recovery impossible.

Formation of Toxic Hydrolysates Following Alkali Burns—Within a few hours after a severe alkali burn, polymorphonuclear cells appear within the conjunctival and episcleral tissues and rapidly penetrate into the substantia propria of the burned cornea. This inflammatory reaction is probably independent of secondary infection, because cultures and bacterial stains ordinarily reveal no pathogens during the first twenty-four hours following a chemical burn. The possibility that a toxic hydrolysate is produced by the action of alkali on the ocular tissues forms one basis for the emergency excision of necrotic conjunctiva and replacement with oral mucous membrane (Deng graft, see later section).

Necrosis of Limbal Vessels—Alkali burns of sufficient intensity to render the limbal region ischemic are usually associated with grave corneal damage. Several clinical cases of chemical injury have been reported in which the initial changes apparently involved only the conjunctiva and sclera and infiltrations and ulceration developed later in the previously clear corneas (Deng, 1904, Thies, 1931, and Schmelzei, 1933). However, there is no experimental evidence that alkali burns involving the conjunctiva and sclera alone produce secondary corneal changes.

The epithelium and endothelium of the cornea are nourished by the bathing fluids with which they are in contact. It is not clear to what extent the viability of the corneal stroma is dependent on the limbal circulation and the diffusion of nutrient substances through the stroma. Mann and Pullinger (1942) reported that mustard gas (dichloroethyl sulfide) burns involving the limbus produce much greater damage to the cornea than burns caused by equal amounts placed on the center of the cornea or on the conjunctiva.

TREATMENT OF ALKALI BURNS OF THE EYE

Many problems arise in consideration of the proper treatment of alkali burns of the eye. Since alkalis penetrate into the anterior chamber within a minute or less after contact with the eye, surface decontamination by means of irrigations would have to be instituted immediately to prevent the development of any corneal lesion. After burns with solid lye or lime, repeated or later irrigations are of value in removing any residual particles of alkali which might be hidden within the conjunctival folds of the cul-de-sacs. The question arises whether first aid with weak acid or buffer solutions is superior to irrigations with water. For lime burns, solutions of various ammonium salts have been highly recommended to remove calcium from the burned cornea. However, it is doubtful whether such calcium deposits are harmful, or whether the ammonium salts effectively extract calcium from the cornea. The practicality of early paracentesis following

ammonia burns has not been properly evaluated. Many alkali burns respond favorably to conservative treatment, while others undergo progressive ulceration in spite of the emergency surgical removal of necrotic conjunctiva and replacement with oral mucous membrane (Denig graft). The experimental and clinical trials with the Denig graft have not been well controlled, and whether its reputed effectiveness is due to an enhancement of limbal circulation or to the removal of necrotized tissue is not clear.

The importance of secondary infection in alkali burns rests largely on the grounds that necrotic tissue furnishes a good bacterial medium and that positive cultures can be obtained from the conjunctival sacs. More recent methods of sterilizing the conjunctival sac have not been tried on eyes burned with alkali. The available experimental data on these questions will be discussed later, with a comparison of the results obtained clinically with conservative measures and with the Denig mucous membrane graft.

Experimental Results of Emergency Treatment—1. *Irrigations with Water or Neutralizing Solutions*. In studies comparing the use of water and that of weak acid solutions (usually 1 or 2 per cent acetic acid) to remove or neutralize alkali which has not yet penetrated into the ocular tissues, most investigators have found that water is more effective (Andrae, 1898-1899, Rosenthal, 1902, Cosgrove and Hubbard, 1928, Leonard, 1927, Brodsky, 1938, Kaplan, 1939). Siegrist (1920) stressed the importance of immediate treatment after ammonia burns. He found that devastating lesions could be prevented by copious lavage with water only if performed within five seconds in young rabbits and within ten seconds in old rabbits after the instillation of 2 drops of strong solution of ammonia. Gummann (1884, cited by Wagenmann, 1911) concluded from his experiments that carbon dioxide water was effective. Yoshimoto (1928) found that he could prevent perforating lesions and leukoma with the use of weak acid solutions or a 1 per cent solution of tannic acid within five minutes after exposure to alkali. In an unspecified number of rabbit eyes burned with 11 drops of 20 per cent sodium hydroxide instilled over a period of ten seconds, Hubbard (1937) found that "75 per cent of the alkali burns treated by irrigation with a weak acid were definitely better than the alkali burn of the opposite eye treated by irrigation with water alone."

In view of the fact that water is probably just as efficacious as weak neutralizing solutions and that speed in beginning treatment is of paramount importance, no time should be lost in an effort to obtain neutralizing antidotes instead of water. After burns with solid lye or lime, the use of weak acid solutions is of value in neutralizing small particles which escape removal by irrigation. For this purpose the

following buffer solution is recommended because its stabilized p_H of 4.5 is well tolerated by the rabbit and the human eye

Glacial acetic acid	2.9 cc (0.05 molar)
Sodium acetate	6.8 Gm (0.05 molar)
Distilled water, q. s.	1,000 cc

2 Solutions to Dissolve Calcium Although it is doubtful that the serious prognosis or residual opacification of the cornea in cases of lime burns is due to the formation of insoluble calcium salts or calcium proteinate, several investigators, acting on the hypothesis that such deposits are formed, have utilized solutions of various ammonium salts in an effort to dissolve and extract such calcium precipitates. Guillery (1902) found that the amount of opacity in excised and *in vivo* corneas burned with lime was reduced by immersion in a solution containing 5 to 10 per cent ammonium chloride in 0.02 to 0.1 per cent tartaric acid. This solution dissolved mercuric albuminate and would, therefore, potentially dissolve any calcium proteinate. Applied as ocular baths of one-half to one hour's duration several times a day, this solution was found to be harmless for the normal human eye. Zui Nedden (1906) burned a portion of each of 16 pig corneas denuded of epithelium with lime and then soaked the specimens in 10 per cent solutions of 16 different salts chosen to dissolve any calcium precipitates. Corneas soaked in ammonium tartrate, ammonium chloride and ammonium chlorate became clearer after five minutes and entirely clear after three hours. Sodium or potassium tartrate did not completely clear the opacity after soaking for twenty-four hours. Ammonium tartrate also cleared corneal opacities due to lead, copper, zinc and aluminum. Early treatment of several lime-burned rabbit eyes with baths of 10 to 20 per cent ammonium tartrate or ammonium chloride twice daily resulted in clearing of the opacity in six to ten weeks. Old opacities covered by corneal epithelium cleared very little after such treatments. It should be remembered that opacification in rabbit corneas has a strong tendency to clear spontaneously, and Zui Nedden did not report the severity of his control lesions nor the degree of spontaneous clearing. Gillessen (1926) found that the lime-burned eyes of 2 dogs treated with 10 per cent neutral ammonium tartrate showed better results than 1 control eye treated with a bland ointment. Alajmo (1929) reported that sodium citrate formed a more soluble and less dissociated calcium salt, and when used early in treatment experiments (rabbits), produced much better results than the tartrate. Antonibon (1931, cited by Pether) found that 8 per cent trisodium citrate was better than 10 per cent ammonium tartrate and that instillation had some beneficial effect even in old lesions. Pether (1939) compared the ability of various solutions to dissolve lime *in vitro*. He passed the various

solutions through 1 Gm of calcium oxide at the rate of 182 cc per minute and obtained the following results

Substance	Molarity	Calcium Oxide Dissolved, Gm /Min	Solution Value Relative to Water
Ammonium chloride	M	0.23	14.8
Ammonium tartrate	M/2	0.08	5.0
Ammonium acetate	M	0.07	5.0
Ammonium citrate	M/3	0.07	4.0
Sodium citrate	M/3	0.06	4.0
Boric acid	M/3	0.02	1.0
Sodium borate	M/6	0.01	1.0
Distilled water		0.01	1.0

A 12 per cent solution of ammonium chloride dissolved almost as much as a 92 per cent solution of ammonium tartrate, 0.026 Gm of calcium carbonate dissolved in 100 cc of the chloride solution after standing four hours, and 0.039 Gm dissolved in the tartrate solution. However, he found that more lime dissolved in stronger concentrations of ammonium chloride and that a solution of 4 per cent could be used without irritation to the human eye. Braun and Haurowitz (1923) stated that calcium carbonate is 567 times as soluble in ammonium lactate as in ammonium tartrate and recommended iontophoresis with the lactate solution to facilitate penetration of the salt. Comparison of the results of iontophoresis of the two solutions using the eyes of 1 rabbit showed no difference in the eventual clearing of the lime opacity. In 2 rabbits with use of ammonium lactate iontophoresis, they found that the eye on which the positive pole was placed eventually became clearer than either the eye on which the negative electrode was placed or the control eye. This finding is somewhat inexplicable in that with the positive pole on the eye the ammonium ions would penetrate into the cornea.

3 Miscellaneous Emergency Measures. Schmidt-Rimpler (1900) recommended the instillation of oily drops to relieve the pain and cover the lime particles. Fortunati (1907, cited by Wagenmann, 1911) recommended the use of a 0.2 per cent trinitrophenol ointment. Sabata (1929) obtained unfavorable results in the treatment of lime-burned rabbit eyes using the following solutions: distilled water, 3 per cent boric acid, 10 per cent sugar solution, 1:4,000 solution of mercuric cyanate, isotonic solution of sodium chloride, 1:2,000 solution of tannic acid and 5 per cent sodium thiosulfate. Best (1930) obtained some favorable results with the use of glycerin and water (1:3) in the treatment of lime burns, the eyes first being cocaineized. Utsumi and Endo (1937) reported 6 cases of severe burns with ammonia gas in which improvement followed treatment with a preparation containing a "detoxifying hormone of the liver," called Yakriton (Sankyo). In the abstract of this article no information is given of the method of preparing

Yakutson Måhlén (1937) reported striking results in 13 patients treated with Pellidol (dimazon or diacetylaminazotoluene salve). This substance is ordinarily used in 2 per cent concentration in a petrolatum base to stimulate the regeneration of epithelium in cases of chronic ulcers. Hubbard (1938) did not obtain any striking results in the treatment of sodium hydroxide burns of the rabbit eye with various solutions designed to provide a more leathery and drier surface and to prevent secondary infection viz, 5 per cent tannic acid, 5 per cent tannic acid with 2 per cent silver nitrate, 1 per cent methylosaniline chloride with 2 per cent silver nitrate and 1 per cent methylosaniline chloride with 5 per cent tannic acid.

4 Paracentesis When Pichler (1910) demonstrated ammonia in the anterior chamber within ten minutes after exposure, he suggested that an emergency paracentesis might, therefore be of value therapeutically. Siegrist (1920) instilled 2 drops of strong solution of ammonia into both eyes of 3 rabbits and one-half to one minute later washed the eyes with a mildly acid solution. A paracentesis was then performed on one eye of each rabbit. Five days later, in the first rabbit the cornea of the eye operated on was entirely clear, whereas the control cornea was completely opaque, in the second rabbit there developed a diffuse, smoky opaque cornea with a small ulcer and hypopyon in the treated eye (no control eye), and the treated eye of the third rabbit showed a heavy opacity in the lower half of the cornea with only faint haziness of the upper half, as compared with the control eye in which there developed a deep yellowish white opacity of the entire cornea with perforation and prolapse of the iris. Since Pichler (1910) found that ammonia was still present in the anterior chamber two hours after the exposure but had disappeared in five hours, one would not expect a paracentesis to be effective after this interval.

Paracentesis has also been recommended by Middleton (1935) and Oaks (1945). The latter obtained pronounced clearing of initially opaque corneas in one eye burned with carbide (containing lime) and a second eye exposed to lye. The first aqueous obtained was opalescent, and paracenteses were repeated by depressing the corneal incision once or twice daily for about one week.

5 Denig Mucous Membrane Graft This operation has been recommended for eyes in which the conjunctiva (especially near the limbus) is extremely necrotized and ischemic. Thies (1941) reserved its use for eyes with reduced sensitivity of the burned cornea. The technic of this operation has been given by Denig (1927), O'Connor (1933), Neuman (1935) and Thies (1938). First, the ischemic conjunctiva and episcleral tissue are completely removed along a 6 to 8 mm strip adjacent to the limbus. Then, a strip of oral mucous

membrane is excised with scissors or the Graefe knife from the inside of the lower lip or cheek, a graft larger than the defect being obtained in order to allow for shrinkage. The epithelial side of the graft can be placed in contact with the gloved finger, and all excess submucous tissue should be trimmed off. The graft is then placed over the denuded sclera and sutured in place along the edges, with perhaps a stay suture through the superficial layers of the sclera and the central portion of the graft to hold it in close apposition with the sclera. A contact lens can be used for this purpose also. The eye is first dressed on the fourth or fifth day, at which time the superficial portions may appear necrotic and grayish white even though the graft is viable. Sutures are ordinarily removed about the twelfth or fourteenth day. Some of the complications which prevent a successful graft are (1) too deep and intensive necrosis of the sclera, (2) application of the graft too late after the injury, i. e., longer than six to eight hours, (3) bleeding under the graft, (4) secondary infection, (5) use of too small or too thick a graft, and (6) overriding of the burned cornea, resulting in adherence of the graft to the cornea.

Tissues other than oral mucous membrane have been used to replace necrotic conjunctiva or to correct symblepharon. Clay and Baird (1936) obtained good results with grafts from the prepuce and the labia minora respectively in 2 cases, but Siegel (1944) concluded from his experience with 3 grafts from the prepuce that they were "conspicuous, have a foul odor and desquamate." The latter author had excellent results in 5 out of 6 cases in which oral mucous membrane was used. De Roth (1940) used fetal membranes obtained at cesarean section, placing the chorionic surface on the wound, with the amnion forming the free surface. These grafts in 8 cases showed a marked tendency to shrink, and the author reserved the use of this material only for cases in which oral mucous membrane was unobtainable. Brown (1941) inserted implants of rabbit peritoneum in order to prevent contact between burned palpebral conjunctiva and the cornea. These implants usually sloughed, and, in discussion of Brown's paper, Masters, Norris and Mann (1941) stated that the peritoneum itself could cause pressure necrosis of normal cornea. Wiener (1943) employed formaldehyde-fixed bovine conjunctiva to correct successfully a total symblepharon in 2 monkeys. From the cosmetic angle, conjunctiva is the most satisfactory tissue for grafting small defects, and this can be obtained from the upper cul-de-sac of the normal eye. Zenkina (1939) obtained conjunctiva from cadavers, not later than eighteen hours after death. The material was kept at a temperature of 2 to 4 C in isotonic solution of three chlorides U S P with 2 per cent dextrose for periods up to four days, and good results were obtained in 10 cases.

The Denig graft (using oral mucous membrane) has been used by its advocates in treating chemical burns of all degrees of severity. Many such burns would have responded equally well to conservative treatment (see compilation of statistics, p 443). It has not yet been satisfactorily demonstrated that alkali burns strictly localized to the limbal conjunctiva and sclera will later involve the cornea, either because of necrosis of the limbal blood vessels or, possibly, because of a toxic hydrolytic product.

Later Treatment of Chemical Burns—At present, the generally accepted later treatment for alkali burns of the eye may be summarized as follows:

1 Atropine Iritis appears within twenty-four hours after any chemical burn which appreciably damages the cornea. The pupil should be dilated early by instilling a mydriatic, e. g., homatropine hydrobromide, 2 per cent, or atropine sulfate, 1 per cent. Although Palic (1928) found that in 26 out of 75 cases of alkali burns the intraocular tension increased, this should not contraindicate the judicious use of mydriatics to prevent posterior synechias.

2 Prevention of Secondary Infection The importance of secondary infection in later ulceration of alkali-burned corneas has not been demonstrated. However, since pathogenic organisms are usually obtainable from culture soon after twenty-four hours have elapsed and necrotic tissue is considered to be a good medium for the growth of bacteria, the prophylactic use of chemotherapy would seem reasonable in all cases of corneal ulceration.

(a) Sulfonamide Ointments Any of the sulfonamide compounds can be made into a satisfactory ophthalmic ointment by mixing finely ground powder into a bland base, such as petrolatum and hydrous wool fat. Sodium sulfadiazine and sodium sulfacetimide are preferable because of their effectiveness against common bacterial contaminants in the eye, their greater solubility in water, their higher penetrating power and the fewer local hypersensitivity reactions. Such an ointment, containing the drug in 5 or 10 per cent strength, should be instilled into the eye every three hours to maintain an adequate level of the sulfonamide compound in the ocular tissues. If the eye becomes irritated or if regeneration of the corneal epithelium appears retarded, the use of the ointment should be discontinued.

(b) Iontophoresis with Sodium Sulfadiazine or Sodium Sulfacetimide Extremely high concentrations of sulfonamide compounds in the cornea and aqueous can be obtained with iontophoresis. Ordinarily, a 2.5 to 5 per cent solution of the sodium salt is placed within the glass iontophoresis container, which fits over the sclera like a contact lens. With the negative pole on the eye, a current of 2 milliamperes

from a 45 volt B dry cell battery is used for about three minutes. This may be repeated about every four hours when it is necessary to maintain a high level of the sulfonamide compound in the treatment of deep corneal ulcers or abscesses.

(c) Penicillin. The instillation of freshly prepared sodium or calcium penicillin (500 to 1,500 Oxford units per cubic centimeter in saline solution or per gram of petrolatum-wool fat ointment base) every few hours will sterilize the conjunctival sac of common ocular contaminants. Higher concentrations of sodium penicillin can be obtained in the cornea with the use of iontophoresis.

(d) Systemic Chemotherapy. For deep corneal ulceration and secondary endophthalmitis, the use of sulfadiazine or sulfamerazine orally or of sodium penicillin intramuscularly is recommended.

3. Prevention of Symblepharon. Severe alkali burns involving the conjunctiva in the cul-de-sacs frequently lead to permanent adhesions between the lids and the globe. Palic (1928) reported that in 31 of his 75 cases of alkali burns complete symblepharon developed. Measures which can be taken to combat this tendency include instillation of oily drops or ointment, frequent breaking of adhesions with a glass rod, insertion of a contact glass or use of a Denig mucous membrane graft. Unfortunately, if the burn has been sufficiently deep, the scarring will progressively obliterate the cul-de-sacs from below in spite of all prophylactic efforts. Permanent symblepharon can then be corrected by the resection of scar tissue and the use of oral mucous membrane or conjunctival grafts.

4. Improvement of Final Visual Acuity. The final reduction in vision is usually due to corneal opacification, irregular astigmatism and, at times, cataractous changes in the lens or secondary glaucoma. Often the irregular astigmatism can be corrected by the use of contact lenses. In suitable cases greatly impaired vision due to the corneal opacity can be improved with keratoplasty. The indications and technic for this procedure have been well outlined by Castroveijo (1941). In general, the reduction of visual acuity of both eyes should be below 20/200, the cornea should not be completely opaque, heavily vascularized or covered by symblepharon and there should be no anterior synechias or secondary glaucoma.

Clinical Results of Treatment of Alkali Burns—Attempts to compare accurately the clinical results of different modes of treatment reported in the literature are difficult for the reasons that the exact degree of exposure to alkali cannot be determined and there are great variations in the time at which treatment was first instituted, in the technic of treatment and in the follow-up examinations of the patient. Essential data for the estimation of the initial severity of the burn are often

not given, and results are frequently classified as "good," "fair" or "poor." There is, also, an unfortunate lack of cases of bilateral ocular burns in which different methods of treatment have been employed on the two eyes. However, a clue to the relative merits of different technics might be obtained by an examination of the reported cases. In addition, 34 cases of burns treated at the Wilmer Ophthalmological Institute are included.

The cases have been arbitrarily divided into three groups according to the initial severity of the burn. Cases of "mild burns" include those in which the initial corrected vision was 0.5 or better or those in which the eye showed only an erosion of the corneal epithelium with faint haziness of the cornea and without any ischemic necrosis of the conjunctiva or sclera. Often it is impossible to obtain an accurate estimation of visual acuity on first examination, and so an estimation of the intensity of the corneal opacity gives a better index of the severity of

TABLE 2—*Results of Treatment of Alkali Burns**

No. of Cases	Severity of Burn	Treatment	Average Final Vision
23	Mild	Conservative	0.80
3		Denig graft	0.83
18	Moderately severe	Conservative	0.83 (S. D. = 0.22)†
9		Denig graft	0.33 (S. D. = 0.23)
10	Very severe	Conservative	0.13
13		Denig graft	0.30

* Summary of cases from the literature and unpublished cases from the Wilmer Ophthalmological Institute.

† S. D. indicates standard deviation.

the lesion. Cases of "moderately severe" burns include those in which the initial vision was 0.4 to 0.1, inclusive, or a corneal opacity was sufficiently dense to blur the details of the iris and fundus and minimal ischemic necrosis of the conjunctiva and sclera was present. In cases of burns classified as "very severe" the initial vision was less than 0.1, with blurring of the pupillary outline and blanching of the conjunctiva and sclera. In table 2 are included only those cases in which the burn was treated earlier than twenty-four hours after the injury, the majority of the burns having been treated by an ophthalmologist within a few hours after exposure. The greater number were due to lime, but a few lye and ammonia burns are included in each group. "Conservative treatment" includes all measures except the Denig graft, viz., irrigations, use of weak acid or buffer solutions, neutral ammonium tartrate or Pellidol, paracentesis, and abrasion of the cornea. In some cases the final vision was estimated from a description of the residual corneal opacity, according to the classification

of cases previously outlined. Follow-up periods varied from several weeks to several months, being essentially equal in the two groups.

The results in table 2 which includes cases from the literature and from Wilmer Institute, suggest that conservative measures may be more effective than the Denig graft for moderately severe alkali burns. The slight difference in favor of the Denig graft for very severe burns is not statistically significant.

Consideration of specific treatments for lime burns only is given in table 3. In the 11 cases of burns treated with "Pellidol salve" reported by Mählén (1937) the corneas were described as initially more or less opaque, without any information as to how much the corneal opacity blurred the media or reduced the vision. Should these cases actually belong to group 3, or the group of "very severe" burns, the results of treatment would be even more striking. Ammonium tartrate appears to be as efficacious as the Denig graft in the treatment of very severe

TABLE 3—*Treatment of Lime Burns**

No. of Cases	Severity of Burn	Treatment	Average Final Vision
6	Mild	Irrigations, etc.	0.82
3		Ammonium tartrate	0.82
5		Pellidol	0.82
5	Moderately severe	Ammonium tartrate	0.68
6		Pellidol	0.80
2		Denig graft	0.20
3	Very severe	Irrigations	0.20
7		Ammonium tartrate	0.31
9		Denig graft	0.38

* Summary of cases from the literature and unpublished cases from the Wilmer Ophthalmological Institute.

lime burns, and several of the patients were not treated with tartrate until several days after the injury. Barkan and Barkan (1924) emphasized that the ammonium tartrate should be freshly prepared and neutralized. It is to be noted that their patients with severe lime burns treated with baths of this agent later required an "abrasion" of the cornea, an operation which the authors stated was made more successful by the previous treatment with ammonium tartrate. Most of their patients with very mild lime burns stated that the period of convalescence and the severity of symptoms were cut in half by the use of this solution. Wagenmann (1911) reported that in some of his patients the lime burns were made worse by treatment with ammonium tartrate and that there were no real beneficial results. De Roth (1929) stated that 29 of his patients with alkali burns would have been considered by Denig and Thies as candidates for mucous membrane grafts but they recovered "good" vision on medical treatment alone. Seventeen patients with mild burns also recovered uneventfully, and 5 patients with very severe burns had final "poor" vision. Winkler (1939) treated 215 patients

with chemical burns (mostly lime burns) along conservative lines irrigations of saline solution every hour for a while, a 2 per cent ethylmorphine hydrochloride salve, homatropine or scopolamine and hot compresses, with the eyes uncovered. Of these patients, 210 recovered, with completely usable vision, mostly 5/7 to 5/4 in each eye. One eye was lost as a result of extensive symblepharon, and 4 eyes with severe lime burns retained vision equivalent to ability to count fingers.

Neuman (1935) reported on a series of 50 cases of chemical burns treated by the Denig graft, the burn being considered "severe" in 30 cases and "very severe" in 20 cases and being caused by alkali in 27 cases (included in the previous tables). During this period, 79 mild burns did not receive a Denig graft. He compared the results in the 50 cases of severe burns with those in 105 cases in which the burns were treated conservatively prior to the time he began using mucous membrane grafts. His visual results were as follows:

No of Cases	Treatment	No Light Perception	Visual Acuity				Symblepharon
			1/60	1/60-1/20	1/10-1/4	1/3-1	
50	Denig graft	18%	6%	10%	6%	60%	10%
105	Conservative	50%	8%	12%	7%	22%	52%

He stated that the best results with the Denig graft were obtained when the operation was performed within four hours after the injury. If it was done later than eight hours after injury, the final results were much worse. Among the 50 cases he reported 5 instances of "failure," evidently referring to the grafts which did not take. Berezninskaja (1940) used the Denig graft on 33 eyes, performing the operation one to twenty-two days after the burn. In 14 eyes the cornea cleared, in 3 eyes the cornea became transparent although the graft sloughed, in 4 eyes the cornea remained opaque, and 12 eyes became blind.

Zenkina (1939) obtained good visual results in 9 cases of alkali burns in which the oral mucous membrane used for transplantation was taken at autopsy fourteen to eighteen hours after death. The grafts were kept in Ringer solution with 0.2 per cent dextrose at 2 to 4 C for twenty-four hours. All but 1 graft took well. Passow (1939) stated that he often dissected out the necrotic conjunctiva and closed the wound without using any graft. Klauber (1932) had 1 case of lime burn in which the corneal epithelium failed to regenerate until he transplanted a conjunctival graft from the opposite eye, four weeks after the injury.

SUMMARY AND CONCLUSIONS

The following summary and conclusions are derived from a review of the literature and from information obtained in studies pursued at the Wilmer Ophthalmological Institute:

Alkali burns are progressive in type, serious late complications frequently developing after little evidence of early involvement. The severity of the lesion is less dependent on the character of the cation than on the concentration of the alkali, the duration of the exposure and the p_H of the solution. The early dense white opacification in cases of lime burns may be due in part to the deposition of calcium carbonate, but it is doubtful whether the calcium ion per se affects the final prognosis. In contrast to acid burns, the mucoid content of the cornea decreases. After lime burns a part of the corneal mucoid is no longer extractable with ammonia.

Conservative treatment is effective for mild and moderately severe alkali burns. This consists of (1) immediate irrigation of the eye with copious amounts of water or any bland solution, (2) a thorough search and removal of any residual particles of alkali hidden within the conjunctival cul-de-sacs, followed by instillations of buffer solution (p_H 4.5), (3) instillation of mydriatics, (4) 10 per cent use of neutral ammonium tartrate (or lactate) as a corneal bath after lime burns (recommended in the literature), (5) instillations of sulfonamide or penicillin ointments to prevent secondary infection, and (6) prevention of symblepharon.

In a small number of reported cases in which early and repeated paracenteses were performed after chemical injury the ultimate clarity of the cornea was considered exceptionally good.

The early excision of necrotic conjunctival and episcleral tissue and its replacement with oral mucous membrane (Denig graft) or conjunctiva has been employed by many clinicians for the treatment of severe alkali burns. Analysis of these reported cases does not reveal any striking benefit attributable to such a procedure.

Wilmer Ophthalmological Institute

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Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

Congenital Anomalies

THE CAUSE AND TREATMENT OF POOR VISION IN ANIRIDIA L G ALGER, *Am J Ophth* 28 730 (July) 1945

Alger believes that the reduced vision associated with aniridia is due to aberration of light in the region of the equator of the lens. He discusses methods used to overcome this and reports a case in which he tattooed the cornea.

W S REESE

MACULAR COLOBOMA WITH BILATERAL GROUPED PIGMENTATION OF THE RETINA I S MCGREGOR, *Brit J Ophth* 29 132 (March) 1945

The anomalies indicated in the title of the article were present in the eyes of a fair-haired youth aged 19 years. In both eyes, all four quadrants of the fundus showed grouped pigmentation of the retina. The sectors or wedges of spots followed the main retinal vessels closely, and the shape of the spots varied from small black dots, near the disk, to larger and paler crescentic, round or polyhedral patches, which tended to fuse with one another nearer the periphery. The base of the wedge did not extend to the equator. In the right eye there was a roughly circular coloboma of the macula, much larger than the disk, with a nonpigmented base and a pigmented border. McGregor regards the condition in this case as a developmental, or inherent, fault, showing arrest and aberration, macular arrest and abnormal development of pigment as a somatic mutation.

W ZENTMAYER

Cornea and Sclera

ISOLATION AND IDENTIFICATION OF THE CAUSATIVE AGENT IN EPIDEMIC KERATOCONJUNCTIVITIS (SUPERFICIAL PUNCTATE KERATITIS) AND HERPETIC KERATOCONJUNCTIVITIS, A E MAUMENEE, G S HAYES and T L HARTMAN, *Am J Ophth* 28 823 (Aug) 1945

The authors reach the following conclusions:

Herpes simplex virus can cause a keratoconjunctivitis which is clinically almost identical with that caused by the epidemic keratoconjunctivitis virus. In spite of the similarity in the clinical picture and the cross immunologic reactions of the two viruses, they are thought to be separate entities, but are probably of the same genus. Intranuclear inclusion bodies produced by the virus of epidemic keratoconjunctivitis have been demonstrated experimentally for the first time. Methylthionine chloride therapy for herpes and epidemic keratoconjunctivitis appears to be of some value in the early stages of these diseases.

W S REESE

A CASE OF INTERSTITIAL KERATITIS AT AN EARLY AGE P J Devlin,
Brit J Ophth 27 155 (March) 1945

In a girl aged 15 months the eyes had become inflamed during the course of a heavy cold. The entire cornea of the right eye was opaque as a result of edematous and cellular infiltration, and a salmon-colored patch had developed. The condition of the left eye was similar, but the infiltration was less intense, and visible keratotic precipitates were present.

Results of the general physical examination were good except for "snuffles" and poor teeth. The mother's Wassermann reaction was positive.

W ZENTMAYER

THE USE OF INSULIN IN THE TREATMENT OF CORNEAL ULCERS T R
Aynsley, Brit J Ophth 29. 361 (July) 1945

Aynsley reports 5 cases and refers to others of various types of ulceration of the cornea which responded favorably to the use of insulin, in 1 case when applied locally and in others when given by injection. The *modus operandi* of the insulin is suggested—the insulin improves the patient's nutrition, it removes some factor necessary for bacterial metabolism, or it increases the rate of epithelial proliferation.

W ZENTMAYER

Injuries

CLINICAL SIGNS AND THERAPY OF INDIRECT INJURIES OF THE EYE
Z A KAMINSKAYA, Vestnik Oftal 22. 7, 1943

Indirect injuries of the eye were as frequent in the recent war as direct injuries. Kaminskaya analyzes cases of ocular injuries obtained chiefly as a result of trauma of the bones of the skull in the neighborhood of the eyeball. There are no external changes, but vision is frequently reduced to a greater degree than with penetrating wounds of the eye. Changes in the eye due to contusion arise most frequently from injuries of the lower lateral margin of the orbit.

The changes in the posterior segment of the eye follow the injury either immediately or later. Complete loss of vision is encountered in cases of large hemorrhages in the vitreous, the latter can occur either with perforation of the posterior limiting membrane or without. If the posterior membrane is not perforated, the vitreous is detached from the *membrana limitans interna*, and preretinal hemorrhages occur. There are also hemorrhages into the retina, near the optic disk or along the large blood vessels, as well as in the macular region. Edema of the macula occurs directly after trauma. The choroid is ruptured frequently with indirect trauma of the eye, the tear is irregular in shape, and a number of ruptures can be seen, indicating that the eye suffers a forceful injury. Injury to the retina is seen in the form of holes in the macula and detachment of the retina, though no detachment from the *ora serrata* has been observed.

The result of large hemorrhages in the vitreous is formation of bands of connective tissue and subsequent detachment of the retina, as well as *synchysis scintillans*. There were observed in the choroid

atrophic patches with pigment, the result of absorbed hemorrhages. Hypotonia of the eye is also one of the signs of the contusion syndrome.

The pathogenesis of contusion of the eyeball, according to Kamin-skaya, lies in the spasm of the blood vessels (as is the case in the brain), in the later phase there is disturbance of permeability of the vessel wall with hemorrhages, followed by formation of connective tissue and secondary detachment of the retina.

The therapy of recent contusions of the eye consisted in the use of vasodilators. Later, since the vessel walls of the injured eye have a greater permeability than those of a normal eye, administration of calcium chloride was pushed in the form of intravenous and intramuscular injections and local ionization. Vitamin C had a beneficial effect. For the absorption of opacities in the vitreous, ionization with ethyl morphine hydrochloride, subconjunctival injections of the drug locally and blood transfusions were used, with favorable results.

O SITCHEVSKA

Neurology

ATROPHY OF OPTIC NERVE PRODUCED BY OPTICOCIASMIC ARACHNOIDITIS C WESKAMP, *An argent de oftal* 5:1 (Jan-March) 1944

Weskamp discusses fully the differential diagnosis of simple atrophy of the optic nerve and emphasizes that in those cases in which objective symptoms are absent and campimetric examination shows a central scotoma in addition to the characteristic peripheral contraction of the field the possibility of opticochiasmic arachnoiditis as the causative factor must be borne in mind. In such cases the ophthalmologist must be on guard and should call in consultation a neurosurgeon, as early operation is of the utmost importance.

Three cases are reported in which such a diagnosis was made through the teamwork of the ophthalmologist and the neurosurgeon. In 1 of the cases the condition was verified by operation.

H F CARRASQUILLO

Orbit, Eyeball and Accessory Sinuses

THE OCULAR NEUROVEGETATIVE SYSTEM. NORMAL INTRAOCULAR TENSION F VIDAL and C S DAMEL, *Arch de oftal de Buenos Aires* 19 212 (April-May) 1944

The authors examined 651 subjects with apparently normal eyes as to their intraocular tension. Tensions were taken but once, in the morning between 9 and 11. The Schiøtz and MacLean tonometers were used. According to their observations, physiologic tension ranges from 15 to 25 mm (Schiøtz). The mean average physiologic tension is 19 mm. Lower tensions, down to 15 mm, belong to persons with physiologic ocular hypotension, and tensions higher, up to 25 mm, are classified as physiologic hypertension. There is a group of patients with unequal tension in the two eyes who deserve special study.

H F CARRASQUILLO

Parasites

OCULAR SYNDROME IN ONCHOCERCIASIS J GRAHAM SCOTT, Brit M J 1: 553 (April 22) 1944

Onchocerca volvulus (the blinding filaria) is commonly found in certain parts of West Africa and America. It produces keratitis and iritis. Strong, Sanground, Bequaert and Ochoa (1934) found microfilarias in affected eyes. Hissette (1932, 1938) described chorioretinitis, retinobulbar neuritis and optic nerve atrophy in cases of onchocerciasis. Luna (1918, 1919) had previously described keratitis punctata onchocercosa due to filarial toxins.

Two cases of onchocerciasis are described in which (1) edema of the upper lid, (2) proptosis, (3) ciliary flush and (4) edema of the optic nerve occurred as unilateral phenomena. The cause is a lymphatic block due directly to microfilarias or indirectly to filarial toxins, as in Calabar swelling. One of these cases is believed to be the only instance of onchocerciasis reported in a Gambian, and the cause of the syndrome is an anaphylactic edema caused by *O. volvulus*. ARNOLD KNAPP

Retina and Optic Nerve

THROMBOSIS OF THE RETINAL, CHOROIDAL, AND OPTIC-NERVE VESSELS
A LOEWENSTEIN AND A GARROW, Am J Ophth 28: 840 (Aug) 1945

Eight cases form the basis of this paper, and the thrombotic changes were found in the vessels of the retina, of the optic nerve and of the choroid. Subendothelial fatty necrosis is frequent and may be found in the choroidal vessels as well. The veins and the arteries are usually involved in the changes.

A newly formed rete mirabile is stained sometimes with a dark blood stain. Chains of aneurysms may show fatty walls.

The central vessels in the optic nerve are often surrounded by a broad sheath of hyaline connective tissue with numerous elastic elements in it. A thrombus resembling a polypus was found in one artery, with lymphocytic infiltration of the wall of the nearby vein. In one artery a mass of exudate, which stained pink with eosin, was found external to a thickened internal elastic coat. The occurrence of a hemorrhage through a rupture in the wall of the vessel could be proved twice histologically. One organized venous thrombus showed endothelial giant cells.

Hemorrhage into the subdural and the subarachnoid spaces around the nerve is common. Some of the hemorrhagic areas are freely sprinkled with blood pigment.

Bruch's membrane may be damaged by a fatty infiltration, and in some places interrupted. Opposite one of these gaps there were damage of the external layers of the retina and a subretinal exudate. It is suggested that this is due to defective filtration through the damaged Bruch membrane.

In 3 of the cases spongy degeneration and cavitation of the optic nerve were found.

A sclerosed plaque was found in one optic nerve, with thrombosed small vessels near its margin, and the thrombosis of these small vessels

is probably the cause of the sclerosed plaque similar to those found in disseminated sclerosis

The plaque may be
W S REESE

News and Notes

GENERAL NEWS

Preceptorships—With regard to the substitution of a preceptorship for a residency in an ophthalmic hospital, the American Board of Ophthalmology has always accepted such training in favorable cases. During the present overcrowding of facilities, the Board expects to take a liberal attitude regarding the requirements for training.

It should, however, be pointed out that neither a residency nor a preceptorship suffices in itself to meet the requirements of the Board. Each case will still be judged on its merits in determining fitness for examination.

In entering on a preceptorship, certain conditions should be kept in mind. First, the student will profit most after a sound course in the basic sciences of physiology of the eye and of vision, optics, pathology, bacteriology, chemistry, pharmacology, the relation of the eye to general disease, anatomy, embryology and neurology. This is essential for a residency, and more so for a preceptorship. While men have been accepted from preceptors not diplomates of the Board, it is obvious that the Board has more information about those teachers who have passed its examinations.

Any preceptor should understand that he is assuming responsibility in taking a student and is not merely obtaining help in the drudgery of his office. He should be willing to give time to clinical training and the use of apparatus, such as the slit lamp, ophthalmoscope and tonometer, and to direction of the student's surgical practice on animal eyes, assisting in operations and ultimately in the performance of them.

To cover the same amount of ground will take much longer in a preceptorship than in a residency, and students should accept opportunities to take hospital positions of all sorts as they become available.

Communications may be addressed to S. Judd Beach, M.D., secretary, Cape Cottage, Maine.

Gonin Medal Award—The Gonin medal was presented on Nov. 3, 1945, to Dr. Paul Bailhart, of Paris, at the University of Lausanne in the presence of the family of Jules Gonin. There were also present Professors Amsler, Buckner, Goldmann, Franceschetti and Streiff, a large number of Swiss oculists, and, from foreign countries, Drs. Weve, Arruga, Faber and Mawas. Addresses were delivered by the rector of the University, by Professor Streiff, in the name of the Faculty of Medicine, and by the president of the Swiss Society of Ophthalmology.

This medal is bestowed every four years. It was given for the first time in 1941 to Professor Vogt.

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President Dr B M Cline, 153 Peachtree St N E, Atlanta, Ga
 Acting Secretary Dr A V Hallum, 478 Peachtree St N E, Atlanta, Ga
 Place Grady Hospital Time 6 00 p m, fourth Monday of each month from
 October to May

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 Secretary Dr Thomas R O'Rourke, 104 W Madison St, Baltimore
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 fourth Thursday of each month from October to March

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 Secretary Dr Luther E Wilson, 919 Woodward Bldg, Birmingham, Ala
 Place Tutwiler Hotel Time 6 30 p m, second Tuesday of each month, September to May, inclusive

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 Secretary-Treasurer Dr Louis Freimark, 256 Rochester Ave, Brooklyn 13
 Place Kings County Medical Society Bldg, 1313 Bedford Ave Time Third
 Thursday in February, April, May, October and December

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 Secretary-Treasurer Dr Sheldon B Freeman, 196 Linwood Ave, Buffalo 9
 Time Second Thursday of each month from October to May

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 September to May

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 Secretary Dr W A Mann, 30 N Michigan Ave, Chicago 2
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 month from October to May

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Chairman Dr D T Vail, 441 Vine St, Cincinnati
 Secretary Dr A A Levin, 441 Vine St, Cincinnati
 Place Cincinnati General Hospital Time 7 45 p m, third Friday of each month
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 Secretary Dr H H Wygand, Guardian Bldg, Cleveland
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 Clerk Dr George F J Kelly, 37 S 20th St, Philadelphia
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 October to May, inclusive

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 Texas
 Secretary Dr L W O Janssen, 710 Medical Professional Bldg, Corpus Christi,
 Texas
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 Secretary Dr Tom Barr, Medical Arts Bldg, Dallas 1, Texas
 Place Dallas Athletic Club Time 6 30 p m, first Tuesday of each month
 from October to June The November, January and March meetings are
 devoted to clinical work

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President Dr H C Schmitz, 604 Locust St, Des Moines, Iowa
 Secretary-Treasurer Dr Byron M Merkel, 604 Locust St, Des Moines, Iowa
 Time 7 45 p m, third Monday of every month from September to May

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 Secretary Dr Wesley G Reid, 667 Fisher Bldg, Detroit 2
 Place Club rooms of Wayne County Medical Society Time First Monday of
 each month, November to April, inclusive

DETROIT OPHTHALMOLOGICAL SOCIETY

President Dr Raymond S Goux, 545 David Whitney Bldg, Detroit 26
 Secretary Dr Arthur Hale, 1609 Eaton Tower, Detroit 26
 Place Club rooms of Wayne County Medical Society Time 6 30 p m, third
 Thursday of each month from November to April, inclusive

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 Secretary-Treasurer Dr Joseph L Holohan, 330 State St, Albany
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 Secretary-Treasurer Dr R H Gough, Medical Arts Bldg, Fort Worth, Texas
 Place Medical Hall, Medical Arts Bldg Time 7 30 p m, first Friday of each
 month except July and August

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 Secretary Dr John T Stough, 803 Medical Arts Bldg, Houston, Texas
 Place Medical Arts Bldg, Harris County Medical Society Rooms Time 8 p m,
 second Thursday of each month from September to June

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 Secretary Dr Kenneth L Craft, 23 E Ohio St, Indianapolis
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 Secretary Dr W E Keith, 1103 Grand Ave, Kansas City, Mo
 Time Third Thursday of each month from October to June The November,
 January and March meetings are devoted to clinical work

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 Secretary-Treasurer Dr Robert G Thornburgh, 117 E 8th St, Long Beach, Calif
 Place Seaside Hospital Time Last Wednesday of each month from October to May

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 Secretary-Treasurer Dr K C Brandenburg, 110 Pine Ave, Long Beach 2, Calif
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 6 30 p m, fourth Monday of each month from September to May, inclusive

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 Secretary-Treasurer Dr J W Fish, 321 W Broadway, Louisville, Ky
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LOWER ANTHRACITE EYE, EAR, NOSE AND THROAT SOCIETY

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 Secretary Dr James J Monohan, 31 S Jardin St, Shenandoah, Pa

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 OPHTHALMOLOGY AND OTOLARYNGOLOGY

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 Place 1718 M St N W Time 8 p m, third Friday of each month from October to April, inclusive

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Each member, in alphabetical order
 Secretary Dr Sam H Sanders, 1089 Madison Ave, Memphis, Tenn
 Place Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital Time 8 p m,
 second Tuesday of each month from September to May

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President Dr Ralph T Rank, 238 W Wisconsin Ave, Milwaukee
 Secretary-Treasurer Dr Frank G Treskow, 411 E Mason St, Milwaukee 2
 Place University Club Time 6 30 p m, fourth Tuesday of each month from October to May

MONTGOMERY COUNTY MEDICAL SOCIETY

Chairman Dr H V Dutrow, 1040 Fidelity Medical Bldg, Dayton, Ohio
 Secretary-Treasurer Dr Maitland D Place, 981 Reibold Bldg, Dayton, Ohio
 Place Van Cleve Hotel Time 6 30 p m, first Tuesday of each month from October to June, inclusive

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President Dr J Rosenbaum, 1396 Ste Catherine St W, Montreal, Canada
 Secretary Dr L Tessier, 1230 St Joseph Blvd E, Montreal, Canada
 Time Second Thursday of October, December, February and April

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Chairman Dr M M Cullom, 700 Church St, Nashville, Tenn
 Secretary Dr R E Sullivan, 432 Doctors Bldg, Nashville, Tenn
 Place James Robertson Hotel Time 6 30 p m, third Monday of each month from October to May

NEW HAVEN OPHTHALMOLOGICAL SOCIETY

President Dr William H Ryder, 185 Church St, New Haven, Conn
 Secretary Dr Frederick A Wiess, 255 Bradley St, New Haven, Conn

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 Secretary Dr Mercer G Lynch, 1018 Maison Blanche Bldg, New Orleans
 Place Louisiana State University Medical Bldg Time 8 p m, second Tuesday
 of each month from October to May

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 Secretary Dr Truman L Boyes, 654 Madison Ave, New York
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 Secretary Dr Benjamin Esterman, 983 Park Ave, New York 28
 Place New York Academy of Medicine, 2 E 103d St Time 8 p m, first Monday
 of each month from October to May, inclusive

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President Dr Harvey O Randel, 117 N Broadway, Oklahoma City
 Secretary Dr S R Shaver, 117 N Broadway, Oklahoma City
 Place University Hospital Time Second Tuesday of each month from Sep-
 tember to May

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OTO-LARYNGOLOGICAL SOCIETY

President Dr A A Steinberg, 1502 Farnam St, Omaha
 Secretary-Treasurer Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha 2
 Place Omaha Club, 20th and Douglas Sts, Omaha Time 6 p m dinner, 7 p m
 program, third Wednesday of each month from October to May

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

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 Secretary-Treasurer Dr J Averbach, 435 Clinton Ave, Clinton, N J
 Place Paterson Eye and Ear Infirmary Time 9 p m, last Friday of every
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PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

President Dr Isaac Tassman, 136 S 16th St, Philadelphia
 Secretary Dr Glen Gregory Gibson, 255 S 17th St, Philadelphia
 Time First Thursday of each month from October to May

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

President Dr Clarence F Bernatz, Park Bldg, Pittsburgh
 Secretary Dr Robert J Billings, Park Bldg, Pittsburgh
 Place Pittsburgh Academy of Medicine Bldg Time Fourth Monday of each
 month, except June, July, August and September

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President Dr Isaac B High, 326 N 5th St, Reading, Pa
 Secretary Dr Paul C Craig, 232 N 5th St, Reading, Pa
 Place Wyomissing Club Time 6 30 p m, third Wednesday of each month from
 September to July

RICHMOND EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Luther C Brawner, Professional Bldg, Richmond, Va
 Secretary Dr Clifford A Folkes, Professional Bldg, Richmond, Va
 Place Westmoreland Club Time 6 p m, second Monday of each month from
 October to May

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Frank Barber, 75 S Fitzhugh St, Rochester, N Y
 Secretary-Treasurer Dr Charles T Sullivan, 277 Alexander St, Rochester, N Y

ST LOUIS OPHTHALMIC SOCIETY

President Dr Vincent Jones, 634 N Grand Blvd, St Louis
 Secretary Dr T E Sanders, 508 N Grand Blvd, St Louis 3
 Place Oscar Johnson Institute Time Fourth Friday of each month from October
 to April, inclusive, except December, at 8 00 p m

SAN ANTONIO OPHTHALMO-OTO-LARYNGOLOGICAL SOCIETY

President Dr Belvin Pritchett, 705 E Houston St, San Antonio 5, Texas
 Secretary-Treasurer Lt Col John L Matthews, AAF School of Aviation Medicine,
 Randolph Field, Texas
 Place San Antonio, Brooke General Hospital, Randolph Field or San Antonio
 Aviation Cadet Center Time 7 p m, second Tuesday of each month from
 October to May

SAN FRANCISCO COUNTY MEDICAL SOCIETY, SECTION ON EYE,
 EAR, NOSE AND THROAT

Chairman Dr Roy H Parkinson, 870 Market St, San Francisco
 Secretary Dr A G Rawlins, 384 Post St, San Francisco
 Place Society's Bldg, 2180 Washington St, San Francisco Time Fourth
 Tuesday of every month except June, July and December

SHREVEPORT EYE, EAR, NOSE AND THROAT SOCIETY

President Dr David C Swearingen, Slaterry Bldg, Shreveport, La
 Secretary-Treasurer Dr Kenneth Jones, Medical Arts Bldg, Shreveport, La
 Place Shreveport Charity Hospital Time 7 30 p m, first Monday of every
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President Dr Clarence A Veasey Sr, 421 W Riverside Ave, Spokane, Wash
 Secretary Dr Clarence A Veasey, 421 W Riverside Ave, Spokane, Wash
 Place Spokane Medical Library Time 8 p m, fourth Tuesday of each month
 except June, July and August

SYRACUSE EYE, EAR, NOSE AND THROAT SOCIETY

President Dr A H Rubenstein, 713 E Genesee St, Syracuse, N Y
 Secretary-Treasurer Dr I H Blaisdell, 713 E Genesee St, Syracuse, N Y
 Place University Club Time First Tuesday of each month except June, July
 and August

TOLEDO EYE, EAR, NOSE AND THROAT SOCIETY

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 Secretary Dr W W Randolph, 1838 Parkwood Ave, Toledo, Ohio
 Place Toledo Club Time Each month except June, July and August

TORONTO ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman Dr W R F Luke, 316 Medical Arts Bldg, Toronto, Canada

Secretary Dr W T Gratton, 216 Medical Arts Bldg, Toronto, Canada

Place Academy of Medicine, 13 Queens Park Time First Monday of each month, November to April

WASHINGTON, D C, OPHTHALMOLOGICAL SOCIETY

President Dr Harold M Downey, 1740 M St N W, Washington, D C

Secretary-Treasurer Dr Richard W Wilkinson, 1408 L St N W, Washington, D C

Place Medical Society of District of Columbia Bldg, 1718 M St N W, Washington, D C Time 7 30 p m, first Monday in November, January, March and May

WILKES-BARRE OPHTHALMOLOGICAL SOCIETY

Chairman Each member in turn

Secretary Dr Samuel T Buckman, 70 S Franklin St, Wilkes-Barre, Pa

Place Office of chairman Time Last Tuesday of each month from October to May

RECURRENT APHTHOUS UVEITIS WITH MUCOCUTANEOUS LESIONS

PROF DR A FRANCESCHETTI

M VALERIO

AND

J BABEL

GENEVA, SWITZERLAND

DURING the last few years a new syndrome has been described in the European literature of dermatology and ophthalmology,¹ a syndrome characterized by periodically recurring uveitis and a group of mucous and cutaneous symptoms, namely, cutaneous eruptions of various types and aphthae and ulcerations of the buccal and genital mucous membranes. This disease is not new, for the first observation seems to have been made by the French oculist Janin de Combe Blanche² in 1772. At the end of the nineteenth century and during the first three decades of the twentieth century a number of isolated observations were published under various titles: catamenial iridochoroiditis (Trousseau³), intermittent hypopyon, or periodic or recurrent hypopyon (Bitsch,⁴ Quaglino,⁵ Neuschuler⁶), septic iritis (Gilbert⁷), recurrent allergic uveitis (Weve⁸), aphthous uveitis (Dascalopoulos⁹), and,

From the Ophthalmological Clinic of the University of Geneva.

1 We could not find any reports on this subject in the American literature up to and including 1942. Later periodicals have not been received in Switzerland.

2 Janin de Combe Blanche, J. *Mémoires et observations anatomiques, physiologiques et physiques sur l'œil*, Lyon, Freres Perisse, 1772, p. 412.

3 Trousseau. *Irido-choroidite catameniale*, Bull. Soc. d'opht. de Paris, 1890, p. 429.

4 Bitsch, W. *Intermittierendes Hypopyum*, Klin. Monatsbl. f. Augenh., 17, 56, 1879.

5 Quaglino, A. *Di alcune forme morbose sculari intermittenti*, Ann. d'ottal. 1, 7, 1871.

6 Neuschuler, A. *L'iridectomia come intervento nell'ipopion recidivante*, Arch. di ottal. 6, 68, 1898.

7 Gilbert, W. *Ueber die rezidivierende eitrige Iridozyklitis (I. septica) u. ihre Beziehungen zur septischen Allgemeinerkrankung*, Arch. f. Augenh. 86, 29, 1920.

8 Weve, H. *Ueber rezidivierende allergische Staphylokokken-Uveitis*, Arch. f. Augenh. 93, 14, 1923.

9 Dascalopoulos, N. *Sur deux cas d'uveite recidivants*, Ann. d'ocul. 169, 387, 1932.

especially, recurring iritis with hypopyon. In a certain number of these observations the coexistence of cutaneous lesions is mentioned. Dermatologists have reported cases of erythema characterized by recurrent ulcerations of the mouth and genital organs, in particular the *ulcus vulvae acutum* of Lipschutz,¹⁰ in which ocular manifestations have been observed. The Turkish dermatologist Behcet¹¹ (1937), recognizing the interdependence of the mucous, cutaneous and ocular symptoms, excluded from the disease the recurrent iritis with hypopyon. The Belgians Weekers and Reginster¹² (1938) defined the entire clinical picture, asserting that it was an independent illness. In 1939 Franceschetti and Valerio¹³ contributed new arguments in support of this conception, with 4 unpublished observations. The studies of Cavara¹⁴ (1940), Schmidt¹⁵ (1940) and Jensen¹⁶ (1941) and the isolated observations of Foss,¹⁷ Gozcu,¹⁸ Paul Knapp,¹⁹ Marucci,²⁰ Schupfer²¹ and

10 Lipschutz, B. Ueber eine eigenartige Geschwürsform des weiblichen Genitales (*Ulcus vulvae acutum*), *Arch f Dermat u Syph* **114** 363, 1912

11 Behcet, H. Ueber rezidivierende, aphtose, durch ein Virus verursachte Geschwüre am Mund, am Auge und an den Genitalien, *Dermat Wchnschr* **105** 1152, 1937

12 Weekers, L., and Reginster, H. Contribution a l'etude de l'iritis recidivante a hypopion (Uveite allergique recidivante a hypopion), *Bull Soc belge d'opht*, 1938, no 76, p 31, Un nouveau syndrome: iritis, ulcères aigus de la bouche et de la vulve, sa parenté avec l'iritis recidivante a hypopion, *Arch d'opht* **2** 697, 1938

13 Franceschetti, A., and Valerio, M. Della associazione di manifestazioni oculari ed in special modo della irite ad ipopion recidivante con affezioni della cute e delle mucose della bocca e degli organi genitali, *Atti Cong di ottal*, 1939, p 291

14 Cavara, V. Nuove osservazioni ed ulteriori ricerche sulla ipopionirite recidivante associata ad alterazioni delle mucose e della cute, *Boll d'ocul* **29** 789, 1940, Ueber ein besonderes Syndrom, gekennzeichnet durch rezidivierende Hypopyoniritis, verbunden mit Geschwüren des Mundes und der Geschlechtsteile und mit Hautausschlägen, *Klin Monatsbl f Augenh* **104** 629, 1940

15 Schmidt, R. Zum Krankheitsbild der rezidivierenden Hypopyon-Uveitis, *Arch f Ophth* **142** 185, 1940

16 Jensen, T. Recurrent Aphthous Ulcerations of Oral Mucous Membrane and Genitals Associated with Recurrent Hypopyon, Iritis and Atrophy of Optic Nerve (Behcet Syndrome), *Ugesk f læger* **102** 1023, 1940, abstracted, *Zentralbl. f d ges Ophth* **46** 446, 1941, Sur les ulcerations aphteuses de la muqueuse de la bouche et de la peau genitale combinees avec les symptômes oculaires (Syndrome de Behcet), *Acta dermat-venereol* **22** 64, 1941

17 Foss, B. Die doppelseitige rezidivierende Hypopyon-Uveitis (Behcets Syndrom), *Acta ophth* **19** 293, 1941, Die doppelseitige ruckfallige Hypopyon-Uveitis (Behcets Syndrom), *Nord med*, 1942, p 2313

18 Gozcu, N. Ueber einige Falle rezidivierender Stomatitis aphtosa durch ein wahrscheinlich ansteckendes Virus, begleitet von Neuritis optici u Iritis, *Turk oftal Gaz* **2** 587, 1938

Delord²² contributed further to this conception. Hugonnier²³ made an interesting synthesis of this disease in his thesis. Touraine²⁴ gave a new interpretation by considering the condition as the most severe manifestation of the general process "aphthosis," which is usually harmless and which is essentially characterized by the appearance of multiple and recurrent aphthae. The abundance of these publications in the lapse of a few years shows that the disease is not rare but that it has not received until now the attention that it deserves.

CLINICAL CHARACTERISTICS

The clinical evolution of this disease is characteristic. It affects young people, generally between the ages of 20 and 30, and evolves slowly over a period of years, both sexes are affected in equal proportions (contradictory to the opinion of certain authors [Weve⁸] that only men are affected). The illness is essentially characterized by its recurrence, and especially by the periodicity of the attacks. The periodicity is not necessarily constant, but is often regular for a given subject. During the period of active illness, it varies from two to three weeks up to several months, with remissions.

In the beginning the lesions are usually cutaneous or mucous in nature, the ocular localization appearing later (a few months to several years), but it is the ocular condition which especially attracts the attention of the physician, as well as the patient, it is the ocular disease that in the end, after having dragged on for a more or less long period, always dominates the clinical picture because of its seriousness.

Buccal and Genital Lesions—The beginning of the illness is insidious and is characterized by the sudden appearance of banal buccal aphthae, with or without submaxillary enlargement of the lymph nodes, sometimes, and apparently more frequently in women, there are attacks of genital "herpes," which may be mistaken for catamenial herpes. The

19 Knapp, P. Rezidivierende Hypopyomyritis, *Ophthalmologica* **96** 297, 1939, Beitrag zur Symptomatologie und Therapie der rezidivierenden Hypopyomyritis und der begleitenden aphthosen Schleimhauiterkrankungen, *Schweiz med Wchnschr* **71** 1288, 1941, Zur Therapie der rezidivierenden Hypopyomyritis und ihrer Begleitkrankheiten, *Klin Monatsbl f Augenh* **108** 502, 1942, Kataraktoperation bei einem Fall von rezidivierender Hypopyomyritis, *Ophthalmologica* **105** 282, 1943.

20 Marucci, L. Uveite ad ipopion ed alterazioni cutanee recidivante, *Boll d'ocul* **29** 355, 1940.

21 Schupfer, F. Sopra un caso di ipopion-irite recidivante con manifestazioni cutaneo-mucose, *Ann di med nav e colon*, 1942.

22 Delord, E. Un nouveau syndrome. Iritis à répétition hémorragies du vitre, ulcères recidivants de la bouche et des organes génitaux, *Ann d'ocul* **177**: 366, 1940.

23 Hugonnier, R. L'uveite recidivante a hypopyon, Lyon, E. Vitte, 1941.

24 Touraine, A. L'aphthose, *Presse med* **28** 571, 1941.

genital involvement sometimes shows itself as small groups of recurrent aphthae, accompanied or not with inguinal enlargement of lymph nodes and, more rarely as the *ulcus vulvae acutum* of Lipschutz. Multiple lesions usually appear on the internal side of the labia majora and labia minora, they have the appearance of little red spots variable in size develop rapidly into ulcerations and are covered at this stage with a strongly adherent gray exudate, recovery takes place in several days, without leaving any scars. Touraine²⁴ expressed the opinion that there is no essential difference between the ulcer of Lipschutz²⁵ and ordinary aphthae. These ulcerations cannot be traced back to a known cause. In men one may find similar aphthae and ulcerations on the scrotum, in the balanopreputial grooves, on the glans or on the prepuce sometimes accompanied with nongonococcic urethritis. The buccal involvement itself is not constantly represented by typical aphthae. In 1 of our cases we noticed painless, wide-spreading ulcerations on the hard palate, which recalled syphilitic mucous plaques. Ulcerations can also be found on the rectal mucosa (a personal case), but they have no relation whatever to Nicholas-Favre disease (*lymphogranuloma venereum*), they may also occur in the respiratory tract (a case of Jensen,¹⁶ with hemoptysis).

Cutaneous Lesions—The cutaneous lesions, which exist in the majority of cases and which usually precede the ocular localization, are also of recurrent character and are particularly striking. Sometimes they appear as erythema nodosum, as papulopustular erythema or as pyodermatitis and sometimes as fugitive painful subcutaneous nodules, such attacks usually coincide with fever.

Touraine²⁴ observed that in cases of aphthosis there are cutaneous lesions with predilection for localization on the scalp which at first simulate acne and later ulcerate. Such lesions are rarely found (Hugonnier²³) in the severe form of the syndrome.

Ocular Syndrome—The ocular symptoms are rarely the first manifestation of the disease. Often the first signs of ocular involvement are photophobia and slight irritation of the eyeball without visual diminution. But later the attacks become more violent and uveitis develops, uveitis which is generally not accompanied with congestion of the conjunctiva or with violent phenomena of irritation. On the other hand, the uveitis is accompanied with considerable deterioration of visual function, due especially to serious opacification of the vitreous. The exudation in the anterior chamber is not always important, at least during the first attacks, and usually clears up within three or

25 Lipschutz, B. *Ulcus vulvae acutum*, in Unna, P., and Rille, J. H. *Dermatologische Studien*, Leipzig, L. Voss, 1923, vol. 25, in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1927, vol. 21.

four days. This does not apply, however, to the opacification of the vitreous, which often persists for two to three weeks. The uveitis generally does not affect both eyes simultaneously but, rather, occurs in one after the other, it is exceptional that it remains unilateral. The entire attack lasts from two to three weeks, and recurrence often takes place at fixed intervals (of three, four or six weeks), or at times more irregularly. There may be prolonged spontaneous remissions, after which the attacks return in their original rhythm. The hypopyon is not a constant element and is usually absent during the first attacks. It is often the case that only at the end of several months or years are the relapses complicated by abundant hypopyon (0.5 to 1 mm), which disappears in two or three days. At the beginning the vision becomes normal again between attacks, a state which may persist for months or years. But sooner or later the visual disturbances become permanent. They are due not only to the opacities of the vitreous but also to a macular lesion of a degenerating microcystic type ("honey-comb macula"). The optic nerve may be attacked, and if ophthalmoscopic examination shows optic atrophy the visual field is concentrically contracted, sometimes after the first attacks. After a lapse of time, which may vary in length, the disease progresses inexorably toward blindness. This evolution is observed in most cases in which the course has been followed for a sufficiently long time. Later the eyeballs atrophy.

In a number of cases the beginning of the ocular syndrome was characterized by a disturbance of the fundus of the eye and not of the anterior parts: posterior uveitis, optic neuritis, macular lesions (Gravemeyer²⁶), as has also been observed with the uveitis of Vogt and Koyanagi (uveitis with alopecia, vitiligo, poliosis and dysacusia [Babel²⁷]).

Between the attacks it happens frequently that the uveitis is not completely dormant, especially in the advanced stage, even if the visual acuity is relatively good, one is able to recognize with the slit lamp a cellular veil over Descemet's membrane and a fairly large number of cells circulating in the aqueous humor and in the vitreous. Some authors have mentioned hemorrhages of the retina or of the vitreous (Weve,⁸ Cavara,¹⁴ Delord,²² Schmidt¹⁵) or a proliferating retinitis (Weve,⁸ Tatar²⁸), sometimes one also observes sheathed retinal vessels.

26 Gravemeyer, E. C. Die Trias von Behcet, *Nederl. tijdschr. v. geneesk.*, 1942, p. 317.

27 Babel, J. Ueber Augensymptome bei der sogenannten Schweinehirttenkrankheit (Maladie des porchers), *Ophthalmologica* 96:159, 1938; Syndrome de Vogt-Koyanagi, *Schweiz. med. Wchnschr.* 69:539, 1939.

28 Tatar, J. Retinitis pseudonephritica und Periarteritis retinae anschliessend an Erythema nodosum, *Klin. Monatsbl. f. Augenh.* 103:84, 1939.

Although uveitis is in general the characteristic feature of the syndrome, some authors have mentioned cases in which only the conjunctiva was affected (Bechet,²⁹ Bechgaard³⁰), in such a case the disease probably exists in an attenuated form, which is not the "great aphthosis" of Touraine²⁴ but an incomplete syndrome localized only in the skin and in the mucosa

Other Features—Other morbid phenomena may sometimes complete the syndrome, such as rheumatoid pains (Gilbert,⁷ Blobner³¹), true arthritis (Weve,⁸ Urbanek,³² our personal case 2), recurrent hydrarthroses (Adamantiades³³), acute articular rheumatism (Schmidt,¹⁵ Cavara¹¹), frequently, dental or multiple focal infection, especially of the tonsils (Weve,⁸ Nakayama,³⁴ Urbanek,³⁵ Adamantiades,³³ von Hippel,³⁶ Dascalopoulos,⁹ Sicharulidze,³⁷ Behcet,³⁸ Tatar,²⁸ Franceschetti and Valerio,³⁹ Marucci,²⁰ Cavara,¹⁴ Foss,¹⁷ and others), syphilis (Adamantiades,³³ Dascalopoulos,⁹ Whitwell,⁴⁰ Cavara,¹⁴ Tatar²⁸), signs of a bacillary infection (Rothenpieler,⁴¹ Planner and

29 Behcet, H Some Observations on the Clinical Picture of the So-Called Triple Symptom Complex, *Dermatologica* **81** 73, 1940

30 Bechgaard, P A Case of Recurrent Aphthous Stomatitis Accompanied by Conjunctivitis and Ulcerations of Genitals and Skin, *Ugesk f læger* **102** 1019, 1940

31 Blobner, F Zur rezidivierenden Hypopyoniritis, *Ztschr f Augenh* **91** 129, 1937

32 Urbanek Zur Frage der Entstehung und Aetiologie der periodisch rezidivierenden Hypopyon-Uveitis, *Ztschr f Augenh* **79** 145, 1932

33 Adamantiades, B Un cas d'iritis a hypopyon recidivant, *Ann d'ocul* **168** 271, 1931

34 Nakayama, N Beitrag zur Kenntnis der pathologischen Anatomie der sog rezidivierenden Hypopyon-Uveitis, *Arch f Ophth* **116** 249, 1926

35 Urbanek. Fall von beiderseitiger rezidivierender Hypopyon-Uveitis, *Ztschr f Augenh* **83** 357, 1934

36 von Hippel, E Ein Fall von Iridocyclitis mit rezidivierendem Hypopyon mit anatomischen Befund, *Arch f Ophth* **128** 272, 1932

37 Sicharulidze, I Zur Frage der rezidivierenden Hypopyoniritis im Zusammenhang mit Erythema nodosum, *Arch oftal (Russ)* **8** 658, 1932, abstracted, *Zentralbl f d ges Ophth* **28** 566-663, 1932

38 Behcet, H Kurze Mitteilung über Fokalsepsis mit aphthosen Erscheinungen an Mund, Genitalen und Veränderungen an den Augen, als wahrscheinliche Folge einer durch Virus bedingten Allgemeininfektion, *Dermat Wchnschr* **107** 1037, 1938

39 Franceschetti, A, and Valerio, M L'uveite recidivante (ad ipopyon) manifestazione parziale di una sindrome muco-cutaneo-oculare, *Rassegna ital d'ottal* **9** 1, 1940

40 Whitwell, G Recurrent Buccal and Vulval Ulcus with Associated Embolic Phenomena in the Skin and Eye, *Brit J Dermat* **46** 414, 1934

41 Rothenpieler, K Sekundäre Cyclitis auf den Wege des Saftkreislaufs-entstanden, *Centralbl f pract Augenh* **22** 304, 1898

Remenovsky,⁴² Nakayama,³⁴ Dascalopoulos,⁹ Sichaulidze,³⁷ Whitwell,⁴⁰ Blobner,³¹ Weekers and Reginster,¹² Wegemer,⁴³ Schmidt¹⁵), less often, tuberculosis (Stahl,⁴⁴ Urbanek⁴⁵), and finally, gastrointestinal disturbances of various kinds, such as alternative constipation and diarrhea, (Adamantiadès,³³ Schmidt,¹⁵ Reiss,⁴⁶ Gilbert⁷) Cavara¹⁴ observed the presence of *Endameba histolytica* in 1 case and chronic enterocolitis in another, Hugonnier²³ mentioned lamblias Carrère⁴⁷ spoke of "intoxication" of intestinal origin, specifying that the term "intoxication" is used in a vague way, in order to eliminate any prejudice with regard to the nature of the disorder

Analysis of the blood does not reveal anything characteristic The blood formula is usually normal, the sedimentation rate is generally accelerated, especially at the moment of the attack and often during the fully active period of the disease

Hugonnier²³ drew attention to an interesting fact In the family of his patient, who had had recurrent aphthous stomatitis since her childhood, the father, otherwise in good health, had repeated appearances of oral aphthae for many years, and her two sisters suffered similarly during their childhood

REPORT OF CASES

Since 1937 we have been able to follow 5 patients who presented the complete syndrome Observations in the first 4 cases have been described in detail by two of us (A F and M V³⁹), we shall recall them only briefly The fifth case has not been published

CASE 1—U F, of Geneva, aged 45, had iritis of the left eye at the ages of 27 and 32 years Since the age of 32 he had suffered from an eczema of the right hand every spring, the healing of which, in 1937, was followed by bilateral iritis From that time on, the patient had had at variable intervals (four to five weeks) attacks of iritis, which soon were complicated by hypopyon The attacks each lasted about one week, hypopyon disappeared in two or three days, between attacks the visual acuity became completely normal again After the third attack the patient drew our attention to the presence of well defined, unpainful, oval ulcerations on the hard palate They disappeared in one week Operation for

42 Planner H, and Remenovsky, F Beitrage zur Kenntnis der Ulcerationen am ausseren weiblichen Genitale, Arch f Dermat u Syph **140** 162, 1922

43 Wegemer Die atypische torpid verlaufende Tuberkulose, Ztschr f Tuberk **84** 267, 1940

44 Stahl, J Zur Frage der endogenen rezidivierenden Hypopyon-Iritis, Klin Monatsbl f Augenh **69** 721, 1922

45 Urbanek Ueber die rezidivierende Hypopyon-Iritis und ihre Beziehungen zur Tuberkulose, Ztschr f Augenh **69** 174, 1929

46 Reiss, W Augenerkrankungen und Erythema nodosum, Klin Monatsbl f Augenh **44** 203, 1906

47 Carrère, M Iridocyclite purulente récidivante, Bull et mém Soc franç d'ophth **44** 345 1931

acute appendicitis, in 1939, was followed by a long period of remission, which led us to believe that the patient was cured. However, ten months later, the attacks recurred at variable intervals. The patient died three years after the beginning of the disease, of an intercurrent disease. We were thus unable to follow the disease to its conclusion.

CASE 2—In the case of Mrs. C., an Algerian, whom we saw for the first time at the age of 41, the illness developed over a period of many years. At the age of 25 she suffered from vaginal, vulvar and rectal ulcerations, which appeared during her menstrual periods. Sometimes they were accompanied with pain and tumefaction of the inguinal lymph nodes. At each new attack her vision became slightly diminished, and sometimes small huccal ulcerations appeared. At the age of 36 she had the first attack of bilateral iritis, and since then she has suffered from a relapse every month, sometimes the right eye, and sometimes the left eye, is the main focus of the attack. The attacks became complicated by hypopyon after the second year. When we saw the patient, in 1938, there were posterior synechias in the right eye and beginning optic atrophy (visual acuity 5/30), the visual field was reduced. In the left eye vision was practically nil, and the eyeball was atrophied. A delayed appendectomy (pyocyanic bacilli in the appen-



Fig. 1 (case 2) —Iritis with hypopyon

dx.) was followed by an aseptic abscess of the wall, which, however, did not prevent, or even postpone, the recurrences. Some months after the patient left the clinic she informed us that, owing to an extremely violent attack, the vision of her right eye had become practically zero. Since the beginning of the disease the patient has suffered from a typical attack of erythema nodosum each spring.

CASE 3—G. F. of Milan, Italy, aged 22, for four years had suffered from attacks of iridocyclitis in both eyes, which repeated themselves at more or less regular intervals and after some months were complicated by hypopyon. The ocular relapse was always accompanied with cutaneous and oral mucous manifestations (acneiform eruptions and recurrent buccal aphthae). There were no lesions of the genital organs. In the case history, one remarked the occurrence of articular rheumatism of the knee at the age of 17 and of dental infections. As in the preceding case, no therapeutic treatment could prevent the evolution toward atrophy of the eyeball and blindness. One eye, enucleated in 1941, showed on histologic examination the usual lesions of chronic uveitis with ossifications of the choroid, but no specific lesions (di Ferdinando⁴⁸).

48 di Ferdinando, R. Studio istologico di un bulbo oculare divenuto atrofico per uveite recidivante ad ipopion, Boll. d'ocul. 22 81, 1943.

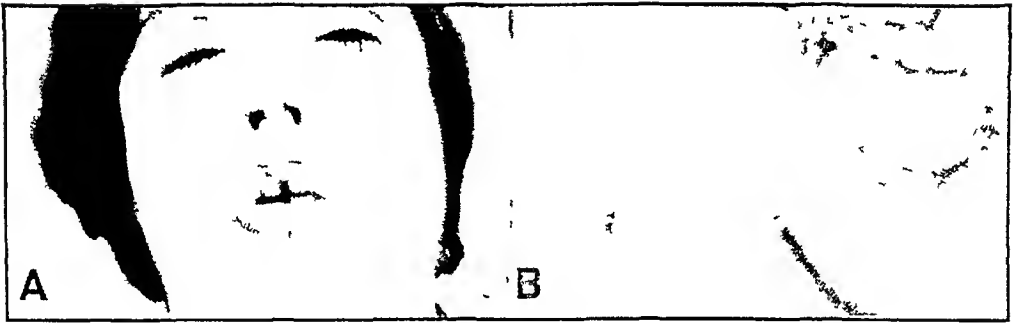


Fig 2 (case 2) —Aphthae on (A) the margin of the tongue and (B) the upper lip

CASE 4—V R, of Reyvroz (Haute-Savoie), at 22 had "conjunctivitis" and at 26 another ocular attack, which caused visual difficulties. A year later these visual disturbances recurred regularly and periodically and seemed to be related to the menstrual cycle (recurrence usually ten days before the menstrual period). With the ocular lesions fugitive genital ulcerations appeared, which recalled catamenial herpes, buccal and large lingual aphthae also appeared. When she was 28, we observed hypopyon for the first time. The visual acuity was permanently diminished because of microcystic degeneration of the macula. When the patient was again examined, at the age of 31, between two attacks, a fine cellular veil, covering the posterior surface of the cornea was observed, and cells in circulation were seen in the anterior chamber and in the vitreous. Vision was 5/40 in each eye.

CASE 5 (unpublished observation, presented before the Medical Society of Geneva, May 25, 1944)—B A was born in 1911, in Lausanne.

Family History—His father was alcoholic and died of peritonitis at the age of 52. His mother was in good health, as were a brother and a sister. One brother died at the age of 12, of diphtheria. The patient's first wife, from whom he was divorced, was in good health, as were a 9 year old son and his second wife.

Personal History—During childhood the patient had repeated attacks of pharyngitis, with frequent furuncles, at the age of 10 he had diphtheria, followed by albuminuria, which lasted six months. There was no history of venereal disease. At 25 he had a serious attack of angina, with amygdalectomy. Since 1936 he had suffered from recurrent buccal aphthae (cheek, palate and tongue). The disease began in June 1936, after an attack of grip, complicated by aphthous stomatitis and gingivitis. Twice aphthae appeared on the genital organs. Since 1936 he had frequently been subject to a disorder of the skin, characterized by the sudden appearance (within several hours) of mobile, subcutaneous nodules the size of a hazelnut, which were painful on pressure and were accompanied with a slight attack of fever. The nodules were often found on the calf of the leg, and also on the arms and even on the face. They lasted about a week, after which they disappeared without leaving any trace. Since 1938 their periodicity had been regular, about every six weeks. The patient remarked that they appeared sometimes after the experience of violent emotion or some fit of contrariness or anger. At times articular pains occurred. In 1938 he had icterus.

Ocular Involvement—In January 1938, for the first time, he was overcome one morning by photophobia, ocular pains and injection of the eyeball, without deterioration of vision, in a few days everything became normal again. These phenomena were reproduced five times during one year. In January 1939 sudden, quasitotal blindness of the left eye occurred, owing to the first serious attack of uveitis. During the following months the uveitis recurred alternately in the left and in the right eye. Numerous examinations (dental, otorhinolaryngologic and hematologic studies and two punctures of the anterior chamber, the first of which revealed 750 elements per cubic millimeter and the second only 20, with hyperalbuminosis) did not reveal the cause of these disturbances. After failure of all treatments, the attending physician, thinking that the condition was probably a tuberculous uveitis, sent the patient to a mountain sanatorium in Davos, where he stayed for two years. Every six weeks during the first year, he had recurrent uveitis, more often in the left eye and sometimes in both eyes simultaneously, sometimes hypopyon was predominant, sometimes it did not appear. Contrary to the general rule, these attacks were often very painful. Between the attacks vision did not return to normal, there was already a macular lesion at this time.

During the second year of his stay in the mountains his condition ameliorated noticeably, inasmuch as the relapses occurred after longer intervals and were less serious. Each attack was accompanied with cutaneous lesions. The researches undertaken to prove a tuberculous origin did not give a conclusive answer: in the roentgenogram only an old hilar nodular process of little importance, could be seen. The specialist (Dr. Werdenberg) considered the bacillary origin doubtful.



Fig. 3—*A*, subcutaneous nodule of the lid, with diffuse infiltration of the subcutaneous tissue and muscle and the area surrounding the nerve. *B* (higher magnification), nonspecific lymphocytic and plasmacytic infiltration surrounding a blood vessel.

We saw the patient for the first time on Dec. 30, 1942, and since we have been able to follow him only irregularly.

Status (Dec. 30, 1942)—The two eyes were in about the same condition. The patient had not had a recurrence for more than six months. The conjunctiva on both sides showed slight hyperemia. The cornea looked normal on the right side, on the left there were folds in Descemet's membrane. There were no

precipitates, but a fine cellular veil was present. The iris was a little atrophied, and the outlines were indistinct, there were no nodules. Posterior synechias occupied nearly one-half the circumference. The pupils were in a state of average medicamentous mydriasis. On the anterior capsule the pigment was disseminated. There were precipitates on the posterior surface of the lens capsule, which was clear. Abundant, dusty cloudiness could be seen in the vitreous. The fundus of the eye was a little dull, especially in the papillomacular region, localized lesions were noted only in the macular region, where the red-free light permitted us to see a microcystic degeneration. Visual acuity was 1/10 in each eye. There was concentric diminution of the visual field (30 to 40 degrees).

For two days there was a subcutaneous nodule on the left lower eyelid, placed in the deep layers, mobile under the skin and a little painful. Similar nodules were seen on the left leg. There were no aphthae. The small subcutaneous tumor of the eyelid was extirpated. Histologic examination showed a conspicuous inflammatory tumor, composed of leukocytes and plasmocytes, infiltrating the subcutaneous tissue and the superficial layers of the orbicularis muscle, which were

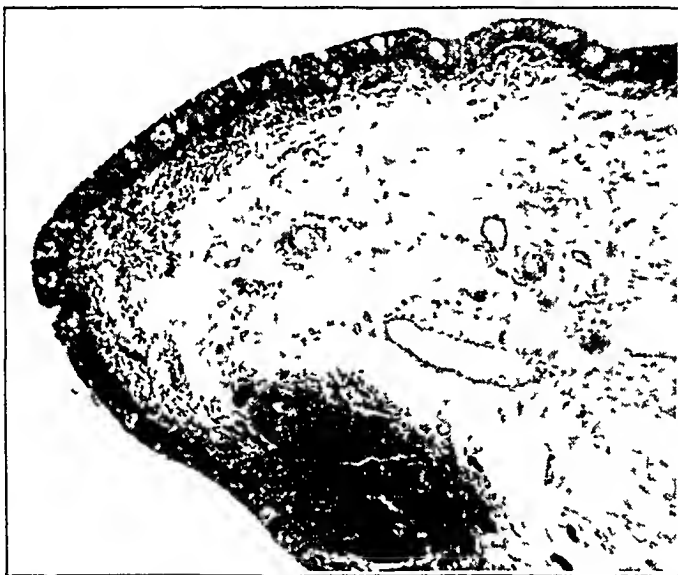


Fig 4—Nodule of the conjunctiva, showing a large lymph follicle, marked hyperemia and considerable interstitial edema. The lymphatic vessels are engorged with red blood cells. There is very slight interstitial infiltration.

dissociated (fig 3), some nerve fibers were enclosed in the tumor. The point of origin seemed to be a follicle. On the slides, stained with the Gram and Ziehl methods, it was not possible to show any micro-organisms. Culture of small fragments remained sterile, and inoculation of a guinea pig gave negative results.

During 1943, at various intervals, both eyes showed signs of irritation, sometimes with deterioration of vision to 1/50. At the time of these attacks, there were fine precipitates on the posterior side of the cornea but no hypopyon, a fine cellular veil was seen on Descemet's membrane, and punctiform opacities were present in the vitreous, during the attacks these opacities were multiplied and gave the patient the sensation of looking through fog. We noted once a few slightly superficial, temporary infiltrations in the right cornea, at another time a conjunctival nodule appeared at the level of the left caruncle. Histologic examination revealed ordinary inflammatory tissue (fig 4). (Inoculation of the

anterior chamber of a rabbit gave fugitive, banal inflammation) Several times during the attacks aphthae and subcutaneous nodules appeared A nodule of the elbow appeared after a venous puncture In 1944 more serious relapses took place, accompanied with hypopyon (in January, April, July and September) During the intervals, even if the eye seemed calm, a cellular veil persisted over the cornea on both sides Visual acuity remained at 1/10 in each eye

Laboratory Examinations—Urine Urinalysis revealed no sugar or albumin, a p_H of 7, a specific gravity of 1.020, traces of urobilin and no sediment

Blood A blood count showed 4,640,000 red cells and 7,200 white cells, with 55 per cent neutrophils, of which 11 were nonsegmented forms, 3.5 per cent eosinophils, 0.5 per cent basophils, 33.5 per cent lymphocytes and 7.5 per cent monocytes The hemoglobin concentration was 92 per cent and the color index 1

The urea measured 26 mg per hundred cubic centimeters

The sugar content of the blood was 80 mg per hundred cubic centimeters The curve of induced hyperglycemia was flat and short (elevation to 102 mg per hundred cubic centimeters one-quarter hour after the ingestion of dextrose [maximum]) At the end of ninety minutes the sugar measured 73 mg, and after one hundred and fifty minutes 65 mg, per hundred cubic centimeters

The reactions to the Wassermann, Hecht-Bauer and Meimcke tests for syphilis were negative, even after reactivation

Blood Proteins The albumin measured 54 Gm, the globulin 30 Gm (albumin-globulin ratio, 1.8) and the total proteins (refractometric method) 78 Gm, per liter The fibrinogen measured 5.7 Gm per liter

The sedimentation rate was variable In 1942 the values were 15, 40 and 105 mm after one, two and twenty-four hours, respectively, in 1944 (March), 5, 28 and 94 mm, and in 1944 (September), 28, 50 and 90 mm

The icterus index (bilirubin) was 12

The reactions of Takata and de Gros (Hayem's fluid) were negative

Agglutination tests for leptospirosis gave negative results in all concentrations

Cutaneous Reactions The Mantoux test gave a positive reaction, with central infiltration, to tuberculin (0.1 cc of dilutions up to 1:10,000)

The cutaneous reaction to histamine was within the normal limits each reaction disappeared at the end of one hour and a half (maximum, five minutes)

Clinical Examination—A complete clinical examination of the patient was made in 1944 in Professor Roch's service, unfortunately not during an attack but at a moment when the clinical symptoms, especially the abdominal, were entirely absent This examination did not reveal anything abnormal in the various systems cardiovascular (electrocardiography), pulmonary (auscultation and roentgenography) and nervous

Gastrointestinal Symptoms—For many years the patient had suffered from digestive troubles, characterized by anorexia chronic constipation, with a saburral state of the superior digestive organs, and occasional diarrhea There was no nausea or vomiting The region of the left hypochondrium was often tender during the attacks of iritis Between the crises, palpation was not painful, and the liver and the spleen had normal dimensions For some years the aphthae seemed to have a relation to alimentary intolerance to certain foods (cheese

chocolate, wine, etc) The roentgenologic examination of the digestive tube, made between exacerbations, did not reveal other anomalies than an atonic stomach, no organic lesions were present, the structure of the mucosa had no pathologic characteristics. Gastric analysis after an Ewald meal showed 75 cc of gastric fluid, 18 degrees of free hydrochloric acid and 28 degrees of total acidity, expressed as cubic centimeters of tenth-normal hydrochloric acid per hundred cubic centimeters of stomach contents, and no lactic acid. Examination of the stool revealed no blood, mucus or parasites. The test meal of Schmidt revealed no sign of any digestive deficiency.

Treatment—Numerous therapeutic measures used in this case did not have any lasting effect, treatment of suspected dental and tonsillar foci, administration of sulfonamide compounds, employment of the usual disinfectants and use of nicotinic amide, were all unsuccessful. Only the climatic therapy seems to have had the effect of delaying the attacks and of making them temporarily less severe and less painful, but it certainly did not bring about a complete recovery.

Résumé—A complete syndrome was seen in a young man, who in his childhood and adolescence was often subject to angina and furunculosis. The onset was with a cutaneous disturbance, which two years later was followed by recurrent, bilateral uveitis, occasionally complicated by hypopyon. There was a spontaneous remission after a two years' stay at high altitude, but recovery did not take place. Visual acuity (1/10) and the visual fields were reduced. No etiologic factor could be discovered. Histologic and bacteriologic examinations of the subcutaneous and conjunctival nodules showed only an ordinary aseptic inflammation. In addition, this patient suffered from gastrointestinal disturbances, which were poorly characterized and which seemed to be aggravated with each recurrence of the cutaneous and ocular process. General clinical examination did not reveal anything of significance and did not contribute any new element to the study of this syndrome.

These five observations are all typical cases of the more or less complete syndrome of recurrent aphthous uveitis, complicated by hypopyon. In each case there are (1) cutaneous lesions of different types (eczema, erythema nodosum, subcutaneous nodules and folliculitis without discernible micro-organisms), (2) lesions of the buccal and genital mucosa (and the rectal in 1 case) of the aphthous type, with the exception of the first case in which there were painless, extensive ulcerations on the hard palate and (3) finally and above all, bilateral recurrent uveitis with hypopyon with a very serious evolution in 3 cases and a milder development in the other 2 cases (1 and 4), in which the patients were followed for a relatively short time.

Furthermore all these cases are characterized by the resistance of the disease to all treatment, other than symptomatic and by the impos-

sibility of finding a precise etiologic agent for them, all research having given negative results

These factors (the one positive, the other negative) which define the clinical picture are for us a proof that the disease is an illness, apparently infectious, due to an unknown agent, which might be a virus, as Franceschetti and Valerio³⁹ have already suggested in the first 4 cases

All these cases fall into the category of the "great aphthosis" of Touraine,²¹ or generalized aphthosis, the most serious form (and the rarest) of a condition which sometimes is characterized only by recurrent aphthous lesions of the buccal or genital mucosa, sometimes by mucocutaneous lesions and, finally, sometimes by multiple symptoms, including cutaneous, mucous, ocular and articular disturbances. The constant character, which permits establishment of the identity of the forms, is the presence of aphthae, which are never inoculable in animals or automoculable and which recur at various intervals for many years. In the generalized form there may be a predilection to certain symptoms, such as polymorphous or nodular erythema, conjunctivitis, uveitis or neuroretinitis, but the conclusive feature of the syndrome is always aphthae, which are never missing

The opinion thus clearly stated by Touraine,²¹ which confirms in outline the opinion of Franceschetti and Valerio³⁹ concerning the nature of the aphthous uveitis, is extremely attractive for it brings some clarity to the solution of the question, which has only been muddled by the multiplicity of the proposed hypotheses. These often contradictory hypotheses do not explain all the cases and often do not resist criticism. This is particularly the case with regard to the theory of tuberculous origin, the validity of which certain authors, following Stahl,⁴⁴ are determined to demonstrate. Stahl based his opinion on the coexistence in his patient of generalized tuberculosis and multiple cold abscesses, which terminated in death. Nakayama,³⁴ Shigeta,⁴⁹ Ito,⁵⁰ and then Urbanek,⁴⁵ having also observed developing bacillary lesions, attributed the uveal condition to the same origin. However, many objections were raised to this interpretation. This coexistence is indeed exceptional (one cannot reasonably regard as significant the sequela of pleurisy or tracheobronchial adenitis, which has been noted by many and which is too common a phenomenon to be considered as an etiologic factor). Besides, the examinations made either on cutaneous lesions or on enucleated eyeballs show only ordinary lesions of subacute or chronic inflammation, without any specific character, so that one is led to admit that it is not a question of a true

49 Shigeta *Nippon Gankwa Zasshi* 28 516, 1924

50 Ito *Nippon Gankwa Zasshi* 25 1082, 1921

tuberculous process but one of an allergic manifestation in a tuberculous patient (The Koch bacillus may, however sometimes produce inflammatory lesions which are manifested not by the typical tubercle but only by a nonspecific infiltration however examinations for the Koch bacillus give constantly negative results in cases of aphthous uveitis)

The idea of a generalized infection with attenuated bacteria, especially the staphylococcus (Weve⁸), must also be considered because of the general aspect of the illness, which presents certain infectious characteristics and because of the frequency of focal infections and cutaneous staphylococcic infections (furuncles) which might be a source of bacterial discharge. But with rare exceptions (a case of Schmidt's,¹⁵ with *Streptococcus viridans* and a case of Adamantiadès',³³ with *Staphylococcus albus*), the hemocultures did not yield pathogens. The radical treatment of infectious foci has never been able to cure a patient, at most one noticed temporary amelioration or prolonged remissions after elimination of a dental granuloma (Marucci²⁰) or appendectomy (case 1). Finally, the numerous attempts at culture or inoculation in various animals, using the aqueous humor (Adamantiadès,³³ Urbanek,⁴⁵ Behcet,³⁸ Cavara¹⁴ and others) or the subcutaneous nodules (personal case 5, Hugonmier,²³ Jensen¹⁶) have always given negative results.

The hypothesis that the disease is due to a virus has principally been defended by Behcet⁵¹ who stated that he had found the proof in the existence of elementary intracellular and extracellular corpuscles in the aphthae of his patient. Franceschetti and Valerio,³⁹ although they were not able to confirm in their cases this observation of Behcet, who still remains the only one claiming to have demonstrated the virus origin of this disease, also consider this etiologic agent probable, or at least possible, the same can be said of Cavara¹⁴. But there, too, the few inoculations of the aphthous material which were tried in the brain of the monkey (Franceschetti and Valerio,³⁹ Cavara¹⁴) or on the cornea of the rabbit did not give the desired proof. Touraine²⁴ expressed the belief that the causative organism is a virus related to that of herpes but different inasmuch as it has never proved inoculable. The absence of leukocytosis and the resistance of this condition to sulfonamide therapy speak in favor of a virus disease. Finally, certain clinical analogies with the bovine aphthous fever, which is due to a known virus transmissible to man (Mach, Babel and Naville⁵²), may lead one to admit an analogous etiology.

51 Behcet, footnotes 11 and 38

52 Mach, R. S., Babel, J., and Naville N. Syndrome muco-cutané avec complications oculaires, *Helvet med acta* 7.552, 1941

Whatever the initial agent may be, it is certain that all the patients affected with recurrent uveitis with hypopyon have the common and constant characteristic of very particular allergic reactions

Allergy is defined as a clinical state of a more or less specific abnormal hypersensitiveness, acquired or congenital, with regard to a determined substance, or allergen. To speak of allergy masks ignorance of the essential nature of the process in question. The hypersensitiveness of the subjects, at first believed to be elective with regard to staphylococcal toxins (Weve⁵), has later been revealed to be nonspecific, in many cases it may be induced by a great number of different agents (see especially the researches of Jensen¹⁶ in 2 cases, in which uveitis was produced by each injection of diluted staphylococcus toxin), and even the simple injection of a physiologic serum or a venous puncture may cause the appearance of a local allergic manifestation (erythema or nodules, Jensen¹⁶, personal case 5). But the fact must be emphasized that generalized hypersensitiveness is not constant and that the reactions to cutaneous tests for allergy may remain negative (Schmidt¹⁵, personal case 1). Urbanek³² stated the belief that the condition represents a hypersensitiveness to foreign proteins.

But although no one can contest the fact that most of the symptoms in the course of the illness can be explained by an allergic reaction (the cutaneous erythema and, especially, the uveal reactions), nevertheless the allergic reaction is of secondary importance and the agent which provokes it is for the moment unknown.

This group of symptoms allows us to connect the aphthous uveitis with the plurifocal erosive ectodermosis of Friessinger and Rendu⁵³ (Berho⁵⁴, Mach, Babel and Naville⁵⁵), which is probably an allergic disease, known in the American literature by the name of Stevens-Johnson disease (Givner and Agelhoff⁵⁵) and in the German-speaking countries by the name of Baader's dermatostomatitis. The symptoms of the two conditions have, indeed, numerous resemblances: cutaneous eruption of the nodular or polymorphous type of erythema with aphthous stomatitis of an acute evolution, lasting a few days, with a tendency to recurrence and participation, besides the skin and the buccal mucous membrane, of most of the mucosae, including the conjunctiva (the ocular involvement is in general superficial, consisting

53 Friessinger, N. and Rendu, R. Sur un syndrome caracterise par l'inflammation simultanee de toutes les muqueuses externes coexistant avec une eruption vesiculeuse des quatre membres, non douloureuse et non recidivante, Paris méd 23 54, 1917

54 Berho, P. Sur une affection febrile a symptomes cutaneomuqueux multiples, Thesis, Lyon, 1941

55 Givner, F., and Agelhoff, H. Stevens-Johnson Disease with Complete Visual Recovery, New York State J Med 41 1762, 1941

in conjunctivitis or more rarely, keratitis, uveitis is exceptional) Another characteristic in common is the certainty of the significance of a generalized allergic reaction. It would be impossible to consider the two diseases as identical, but it is interesting to note the similarity of symptoms in two conditions in which the allergic reactions play such an important, if not essential, part.

Another argument in favor of the allergic nature of recurrent aphthous uveitis can be found in the fact that a certain number of patients showed gastrointestinal disturbances which could not be associated with a toxic, infectious or parasitic etiologic agent (ameba or lamblia). Now, it is known that cases of gastropathy or enteropathy of allergic origin (the antigen, usually alimentary, may sometimes be of another origin, such as pollen) are far from being exceptional. Furthermore, the symptoms in such cases are not specific and can simulate truly organic diseases, such as ulcers, appendicitis or enteritis, according to the seriousness and localization of the allergic manifestations. Although the latter take, in certain patients, an acute, and sometimes dramatic, form (state of shock, cardiovascular collapse, "abdominal migraine"), the chronic state seems more frequent and is manifested by a predominance of spasms with constipation, as well as by diarrhea. In most cases there is alternating diarrhea and constipation, combined with gastric symptoms (nausea, malaise, epigastric pain). The allergic nature is easy to recognize if at the same time there are other cutaneous signs (urticaria, Quincke's [angioneurotic] edema), asthma, nasal hyrorrhea or migraine, but this is not always the case (Urbach,⁵⁶ Paviot and Chevallier⁵⁷). One also finds an increase in the percentage of histamine in the blood in these cases, in which a reaction to antihistamine agents exists. The gastrointestinal manifestations, observed by some authors during the development of aphthous recurrent uveitis, may belong to the allergic digestive disorders (cases of Adamantades,⁵³ Carrere,⁴⁷ Cavara¹⁴), such as anorexia, abdominal pain, irregularity of the bowels and mucus in the stools. In our last case chronic constipation was present, and sometimes diarrhea, with persistent pain in the right iliac fossa, phenomena which increased in a striking way during the attacks of uveitis or when the aphthae and the subcutaneous nodules appeared. The roentgenologic and laboratory examinations, which, unfortunately, were made during an interval between attacks, did not reveal anything pathologic. It is hardly probable that the gastrointestinal disturbances were manifestations of a localized aphthous lesion of the entire digestive tract. In the

56 Urbach, E. Affections allergiques du tractus gastro-intestinal, du foie, et de la vésicule biliaire, *Rev. med.-chir. d. mal. du foie* **11** 116, 1936.

57 Paviot, J., and Chevallier, R. Les gastropathies allergiques. *J. de méd. de Lyon* **17** 31, 1936.

only case in which a gastroscopic study had been done, one found not the supposed aphthous gastritis but an apparently normal mucosa (Hugonnier²³)

The existence of digestive disturbances only contributes one more element to the syndrome and does not solve the question of the origin of the allergy. Indeed, there are two possibilities: either the gastrointestinal disorder is the cause of all the other symptoms and produces the aphthae and the cutaneous and ocular reactions, an assumption which might be proved by the success of the gastrointestinal treatment (only the case of Carrere gives an inkling of proof in this respect), or a similar, unknown, cause produces both aphthous uveitis and the associated symptoms and the digestive disturbances.

A point on which it would seem interesting to insist is the connection between the aphthous uveitis and different forms of chronic and infectious rheumatism, such as Still-Chauffard disease (multiple rheumatoid arthritis), ankylosing spondylarthritis and Reiter's syndrome, or the conjunctivouretrosynovial syndrome. These three forms have the following common characteristics: their chronic, progressive course and the frequency of recurrent uveitis, especially in the first two forms (uveitis occurs in spondylarthritis in an acute form, sometimes even with hypopyon). One is often able to recognize an initial causal agent: the gonococcus for the spondylarthritis, dysentery bacillus for Reiter's syndrome, and infectious disease for the Still-Chauffard disease. But factors other than the causal agent are present and the allergic character is striking. The micro-organism which produces the disease cannot be found either in the uvea or in the articulations; on the other hand, spondylarthritis may exist without initial gonorrhea and the syndrome of Reiter without dysentery—proof that a microbic infection is not sufficient to explain the entire pathogenesis of the syndrome. Like all the other rheumatic conditions, these forms are also considered allergic reactions of the mesenchyme, which in the course of infectious rheumatism produce characteristic, histologic lesions (nodules of Aschoff, subcutaneous nodules of Meynet).

All these facts are arguments which lead us to include recurrent aphthous uveitis in the group of allergic diseases.

These various syndromes have many elements in common, and though the causes differ the pathologic manifestations in the different tissues of the organism, in particular of the eye, are similar. Perhaps one may find another argument in favor of the allergic pathogenesis of the iritis with hypopyon in the histologic examination of the eyeballs if the statements made by Schmidt are confirmed in additional cases. Schmidt¹⁵ has, indeed, described fibrinoid necrosis of retinal arterioles

and a predominance of lesions in the neighborhood of the vessels, as can be found in many forms of rheumatism

Another interesting fact is the striking resemblance of the clinical picture of recurrent aphthous uveitis to the recurrent ophthalmia of horses, the chief symptom of the latter is also a recurrent uveitis with hypopyon, ending in blindness, with atrophy of the eyeball. It seems hardly probable that it is the same disease, which is transmitted from horse to man, as Dor⁵⁸ suggested, but the source of contamination has not been discovered. In spite of numerous researches undertaken by veterinarians and bacteriologists, the etiologic agent of recurrent ophthalmia of horses has never been elucidated—whether a virus infection, brucellosis (Burky⁵⁹), allergic reaction, hereditary illness (Fomynich⁶⁰) or intestinal infection with flagellates or protozoans, especially amebas (Mills⁶¹). This disease, like the aphthous uveitis, could not be produced in other species of animals by inoculation. To explain the nature of the disease, one must fall back again and again on the same theories.

Finally, *Leptospira*, recently in the limelight, was revealed as the causative agent of various forms of meningoencephalitis, attributed hitherto to an unknown virus. This is the case of the "meningitis of the swineherds" (*maladie des porcheirs*) (Gsell and Rimpau⁶²), which, like other leptospiroses, such as Weil's disease, may be complicated by uveitis (Babel²⁷). It is hardly likely that in a disease as chronic as recurrent uveitis with hypopyon an agent which usually produced an acute illness could be incriminated, however, the hypothesis is to be retained, and research along these lines would be useful (negative reaction to agglutination tests in case 5).

TREATMENT

To our actual knowledge, the treatment of aphthous uveitis is extraordinarily deceiving. Ignorant as one is of the exact nature of the illness, there is no specific treatment to follow. All possible treatments have been tried, without ever achieving a lasting result. If one or the other among them seem to have been useful to an author, the same treatment was only a disappointment to those who tried it.

58 Dor, in discussion on Carrere,⁴⁷ p. 352

59 Burky, E. L., Thompson, R. R., and Zepp, H. M. Role of *Brucella* in Human and Animal Ocular Disease, with Special Reference to the Periodic Ophthalmia in Horses, *Arch. Ophth.* **22**:709 (Oct.) 1939

60 Fomynich, V. N. Periodische Augenentzündung beim Pferd in der Krim, *Sovet. vet.* **16**:64, 1939

61 Mills, L. Ocular Disease Occurring in Course of Nondysenteric Amebiasis, *J. A. M. A.* **87**:1176 (Oct. 9) 1926

62 Gsell, O., and Rimpau, W. Feldfieber Meningitis in der Schweiz, *Schweiz. med. Wchnschr.* **74**:208, 1944

afterward Neither the radical treatment of focal infections, nor blood transfusions, especially praised by Urbanek,⁶³ nor sulfonamide therapy (in spite of the good results of Paul Knapp¹⁹ and Weekers and Register¹²), nor desensitization, nor the numerous antiseptic, specific and nonspecific therapeutic methods, nor the gastrointestinal treatment was able to stop the inexorable course of an essentially chronic disease, at most, temporary ameliorations were observed, but never an actual cure, it is also to be recalled that sometimes there were spontaneous remissions This inefficiency of treatment is comprehensible if one admits that aphthous uveitis is due to a virus and that there is no really efficacious treatment of virus diseases except for a few, such as rabies

CONCLUSION

The study of these 5 typical observations allows us to make the clinical picture of recurrent aphthous uveitis more precise and to confirm the statement that it is indeed an independent disease, defined by the development of periodic attacks by its complex and characteristic symptoms and by its resistance to treatment Although it is a disorder which interests the dermatologist as much as the internist, it is above all an ophthalmologic problem, since the most serious symptoms are ocular, which end, in the majority of cases, in blindness after a varying lapse of time

Of the various hypotheses which have been considered to explain the origin of the illness, that of a virus infection seems the most probable, as Behcet,¹¹ Franceschetti and Valerio,³⁰ Cavara¹⁴ and others have admitted This theory finds new support in the concept recently advanced by Touraine,²⁴ who considers aphthous uveitis as the severe and malignant form of "aphthosis," probably due to a virus but not transmissible, this distinction would mark the difference between aphthosis and herpes, which has other analogies with the supposed virus of aphthous uveitis The diseases due to viruses develop in general in an acute form and produce a lasting immunity as with measles and poliomyelitis Only herpes and, sometimes, herpes zoster, which are caused by related viruses, do not produce immunization but, on the contrary, have a great tendency to recurrence

Although a virus explains in a fairly plausible way (since its existence cannot be proved with certainty, the inoculations having failed to produce the disease) the aphthae and the uveitis, it is necessary to introduce another factor, which is the sensitization of the organism This allergy, however, seems to be secondary, and not the initial cause of the disease this is analogous to the ocular disorders of the rheumatic

⁶³ Urbanek Bluttransfusion bei einer beiderseitigen rezidivierenden Hypopyon-Iritis, *Ztschr f Augenh* 85 262, 1935

type (ankylosing spondylarthritis, Reiter's disease, Still-Chauffard disease) in which allergy modifies secondarily and complicates the primary disease due to a determined agent. Allergy alone does not explain aphthous uveitis, with its various symptoms. One might say that aphthous uveitis is an "aphthosis" developing in a sensitized organism.

Finally, the third factor to be remembered is the extremely frequent coexistence of gastrointestinal disturbances, of which one cannot tell whether they are primary, and the cause of the entire illness (one might admit, in this case, the penetration of a virus through the mucosa of the digestive tract), or whether they are secondary, and due to the same cause which produces the other symptoms.

It seems indispensable to us that in the future the etiologic researches should be directed toward identification of a possible virus and that perhaps attempts be made to inoculate animals, which previously have been sensitized to foreign proteins or to various microbic toxins.

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NUMMULAR KERATITIS AND OCULAR BRUCELLOSIS

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IN a previous paper published in collaboration with Guyton,¹ the statement was made that there was reason to believe that in some instances nummular infiltrates in the cornea, the so-called nummular keratitis Dimmer, might be due to an infection with *Brucella*. Since the presentation of this paper several further observations have been made which strengthen this opinion. The clinical and experimental observations which prompt this belief are here presented.

HISTORICAL REVIEW

The term "nummular keratitis" was first used by von Stellwag in 1889² to describe a form of keratitis characterized by a relatively acute onset and the occurrence of multiple, round, sharply delineated, grayish or yellowish white areas, about 0.5 to 1.5 mm in diameter, throughout the various layers of the cornea. These areas were often elevated and had a tendency to break down and ulcerate. There was marked general inflammatory reaction and often vascularization. The course of this disease was rapid, healing usually occurring in twelve to fourteen days and leaving no residue. The disease was usually bilateral.

Shortly after the publication of von Stellwag's paper, there appeared reports by Adler³ on "keratitis sub-epithelialis superficialis," by von Reuss⁴ on "keratitis maculosa" and by Fuchs⁵ on "keratitis punctata superficialis." Adler and von Reuss concluded that the conditions described by them were identical with von Stellwag's "nummular keratitis," while Fuchs, although recognizing the similarity of keratitis punctata superficialis to the disease described by von Stellwag, never-

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1 Woods, A. C., and Guyton, J. S. The Role of Sarcoidosis and Brucellosis in Uveitis, *Arch Ophth* **31** 469-480 (June) 1944.

2 von Stellwag, K. A Peculiar Form of Corneal Inflammation, *Wien klin Wchnschr* **2** 613-614, 1889.

3 Adler, H. Keratitis Subepithelialis, *Centralbl f prakt Augenh* **13** 289-295 and 321-327, 1889.

4 von Reuss. Keratitis Maculosa, *Wien klin Wchnschr* **2** 665-666, 1889.

5 Fuchs, E. Keratitis Punctata Superficialis, *Wien klin Wchnschr* **2** 837-841, 1889, Ringform and Disciform Keratitis, *Klin Monatsbl f Augenh* **2** 513-523, 1901.

theless emphasized that there were points of difference in the two diseases and that they might not be identical

In 1905, under the name of "nummular keratitis," Dimmer⁶ reported 4 cases of a peculiar unilateral keratitis. He summarized the salient features of this keratitis as follows

a disease beginning with pain, photophobia and lacrimation, without secretion, and characterized by the formation of peculiar infiltrates in the cornea. These lie mostly in the superficial layers but may involve the middle layers and usually reach the size of 1 to 1.5 mm. The margins are fairly sharp, there is a tendency to confluence, and opacities several millimeters in size may develop. While some of the areas may be completely reabsorbed, others form round, umbilicated ulcers.

The course drags out. Only in 1 case was the disease bilateral.

Dimmer expressed the belief that this condition was entirely different from forms of keratitis previously described by Adler, von Reuss and Fuchs. He could not identify his cases with those of von Stellwag and stated that they constituted a separate clinical entity. There was a history of injury in only 1 of his 4 cases, and Dimmer therefore concluded that the disease was an endogenous infection of the cornea.

Nothing further of any importance on this subject appeared until 1928, when Salzmann⁷ reported 50 cases of a peculiar keratitis, all from the vicinity of Graz. He stated that he had not observed such cases during his teaching in Vienna. He did not give a detailed description of his cases but stated that in the main they were similar to Dimmer's cases, characterized by a long, drawn-out course and the occurrence of nummular infiltrates throughout the cornea which had a tendency to break down and ulcerate, other areas healing apparently by subepithelial absorption. Salzmann emphasized that the patients were mostly farmers. He expressed the belief that the disease was related to herpes. Twelve of his patients gave a history of preceding ocular trauma.

In 1933, under the name of nummular keratitis, Aust⁸ reported 27 cases. He stated the belief that the condition in these cases, and in the cases reported by Salzmann, was identical with the disease reported by Dimmer and proposed the name "keratitis nummularis Dimmer," adding the name of Dimmer to avoid any confusion with the disease described by von Stellwag in 1889, which he stated was entirely different. Aust's description of the disease is detailed. He described it as a disease of seasonal incidence, reaching its height in August and September, occurring chiefly in young agricultural workers and being usually uni-

6 Dimmer, F. Nummular Keratitis and Its Related Corneal Inflammation, *Ztschr f Augenh* **13** 621-635, 1905

7 Salzmann, M. Keratitis in Connection with Herpes, *Ber u d Versamml d deutsch ophth Gesellsch* **47** 303-308, 1928

8 Aust, O. Keratitis Nummularis (Dimmer), *Arch f Ophth* **129** 576-595, 1933

lateral In 7 of Aust's 27 cases there was a history of preceding trauma The onset of the disease was slow, and in most cases the patient sought medical advice from four to six weeks after the appearance of symptoms There were never inflammatory or irritative conjunctival symptoms The salient feature of the disease was the occurrence of multiple nummular infiltrates throughout the superficial layers of the cornea, in various stages of development These areas were usually 1 to 1.5 mm in size, although they were sometimes much larger On examination with the slit lamp, the single areas were seen to consist of numbers of very fine dots, the intensity of the resulting nummular opacity depending on the arrangement and depth of these dots These opacities were sometimes so superficial that they elevated the epithelium They usually underwent subepithelial absorption with a "sinking in" of the overlying epithelium and the formation of a depressed facet, a picture which Aust found to be the usual one, rather than the ulceration previously described These depressions occasionally persisted for years Careful microscopic study with the slit lamp revealed at times fine stripes or pathways between the different opacities These lines might quickly disappear The course of the disease was torpid In search of the etiologic agent in the disease, Aust made cultures and corneal inoculations in animals of nummular infiltrates, without any results Microscopic examination of an excised area of infiltrate showed proliferation of the fixed keratogerminal cells Aust was unable to name any etiologic agent He expressed the belief that the disease had no relation to herpes Basing his ideas on the seasonal incidence, the definite history of trauma in many cases and the stripes or pathways he sometimes detected between the various corneal infiltrates, he expressed the view that the disease was probably due to some parasite or fungus of grain, which gained entrance to the corneal parenchyma through an abrasion in the cornea, of which the patient might often be unaware, and progressed from one area of the cornea to another along the stripes or pathways between the various infiltrates

In 1934 Salzmann⁹ reported a further series of 82 cases of "nummular keratitis," 13 of which were described in detail In this paper Salzmann went minutely into the general symptomatology of the disease but added little to the previous description of Aust He noted that the disease occurred predominatingly in farm workers and was usually unilateral In 24 of his cases there was a history of preceding trauma, and in 14, a history of preceding colds Salzmann emphasized the points of similarity of keratitis nummularis, keratitis punctata superficialis and keratitis disciformis He expressed the belief that nummular keratitis

⁹ Salzmann, M Keratitis Nummularis Dimmer, Arch f Ophth **132** 399-420, 1934

belonged in this general group of corneal diseases and stood midway between keratitis punctata superficialis and keratitis disciformis and that it might be remotely related to herpes simplex of the cornea or to keratitis dendritica. The fact that a virus origin had been demonstrated for the latter conditions led Salzmann to believe that a similar etiologic agent would later be demonstrated for allied corneal conditions, such as nummular keratitis.

Two cases of nummular keratitis Dimmer were reported by Šácha¹⁰ in 1933. The disease in the first of these cases appears identical with the previously recognized condition, but that in the second case, which Šácha called an atypical form, strongly suggests typical epidemic keratoconjunctivitis. In 1935 Szekeley¹¹ reported 25 cases of nummular keratitis and emphasized its relationship to keratitis disciformis and superficial punctate keratitis. Jese,¹² in 1936, reported 77 cases from Yugoslavia, occurring chiefly among farm workers. The peak incidence of the disease occurred in July. The condition was usually unilateral and had all the symptoms previously described by Dimmer, Aust and Salzmann. Jese stated that the disease was often associated with colds, bronchial catarrh and influenza-like sickness. In 9 of his cases there was a preceding history of trauma. Jese emphasized the similarity of the curve of incidence of the disease to similar curves for herpetic disorders of the cornea and expressed the belief that nummular keratitis belonged to this group of diseases, being a "new form." Again, in 1938, Jese¹³ reported 47 additional cases, all with the same general symptoms, usually unilateral typical nummular infiltrates in the cornea, absence of conjunctival symptoms, prolonged course, occasional ulceration but usually subepithelial absorption with formation of facets. He was unable to confirm the presence of any of the connecting pathways between the corneal lesions previously described by Aust. Jese reaffirmed his belief that the disease was of virus origin and represented a condition midway between herpes simplex and zoster infections. Elwyn,¹⁴ in New York, reported 4 cases in 1935, Chen,¹⁵ in China,

10 Šácha, A. Keratitis Nummularis (Dimmer), *Arch f Ophth* **131** 102-107, 1933.

11 Szekeley, J. Keratitis Nummularis (Dimmer), *Arch f Ophth* **134** 184-188, 1935.

12 Jese, L. Nummular Keratitis, *Klin Monatsbl f Augenh* **96** 219-226, 1936.

13 Jese, L. Nummular Keratitis, *Klin Monatsbl f Augenh* **100** 874-891, 1938.

14 Elwyn, H. Three Cases of Keratitis Nummularis (Dimmer), *Arch Ophth* **13** 1119-1120 (June) 1935.

15 Chen, W. Y. Keratitis Nummularis (Dimmer's Disease), *China M J* **48** 682-690, 1934.

reported 1 case in 1934, and Weskamp and Cotlier,¹⁶ in Argentina, reported 4 cases in 1940

A somewhat similar keratitis, but described under various names and occurring in the form of mild epidemics, has been described from various quarters of the world Herbert,¹⁷ in 1901, described an epidemic of superficial punctate keratitis associated with an encapsulated bacillus which occurred in Bombay in September 1900 The condition was usually unilateral, and the corneal lesions suggested those later described by Dimmer However, in all these cases there were pronounced conjunctival symptoms In 1920 Kirkpatrick¹⁸ described under the term "epidemic macular keratitis" a disease he observed in Madras, India The disease was always unilateral and occurred in all classes of people There were no associated conjunctival symptoms Kirkpatrick's description of the disease is not sufficiently detailed to allow any identification In general, however, it does suggest the disease described by Dimmer, Salzmann, Aust and Jese In 1938 Mulock Houwer¹⁹ reported "about 70" cases of keratitis occurring among agricultural workers in Batavia, Netherland East Indies He expressed the belief that these cases were similar to the cases described by Dimmer and were probably the same as those described by Kirkpatrick and Herbert The condition had been recognized in Batavia as early as 1912 and had been described by Westhoff²⁰ as "sawah-keratitis" Mulock Houwer¹⁹ described the condition in his cases as almost invariably unilateral, usually with a history of some minor preceding trauma, insidious onset, a protracted course, round superficial infiltrates in the cornea consisting of a number of fine dots, the occurrence of facets, occasional ulceration and vascularization Occasionally the corneal infiltrates were larger, up to 3 or 5 mm, and lay deeper in the cornea Only rarely was there any conjunctival discharge or symptoms of conjunctival irritation While he did not make etiologic studies, he apparently inclined to Salzmann's view of a virus origin

Again similar to the aforementioned cases, but reported under the name "nummular keratitis Dimmer" to describe the corneal lesions, are the cases recorded in a series of papers published in Germany from 1938 to 1942 During this period there occurred in Germany and the

16 Weskamp, C, and Cotlier, I Keratitis Nummularis of Dimmer, *An argent de oftal* **1** 256-259, 1940

17 Herbert, H Superficial Punctate Keratitis Associated with an Encapsulated Bacillus, *Ophth Rev* **20** 339-345, 1901

18 Kirkpatrick, H An Epidemic of Macular Keratitis, *Brit J Ophth* **4** 16-20, 1920

19 Mulock Houwer, A W Keratitis Nummularis (Dimmer), *Nederl tijdschr v geneesk* **82** 4152-4156, 1938

20 Westhoff, C H A Keratitis Punctata Tropica, *Centralbl f prakt Augenh* **36** 289-293, 1912

Balkan states an epidemic of keratoconjunctivitis which on retrospect appears identical with the recent epidemic of "shipyard conjunctivitis," now generally known as epidemic keratoconjunctivitis, the virus origin of which has been established and the relation to other virus infections of the cornea studied. Schneider²¹ called attention to these cases before the Munich Ophthalmological Society in 1938. Later, Meissner²² described the epidemic as one of "keratitis nummularis Dimmer." Senger²³ described the condition as a conjunctival disease of unknown cause, and Schwitalla²⁴ as "epidemic keratitis nummularis Dimmer" in 1939. The disease as described by these authors is characterized by intense edema of the lids, conjunctival symptoms, subepithelial corneal infiltrates, diminution of corneal sensitivity, usually involvement of the preauricular and regional lymph nodes and a high degree of transmissibility. This epidemic disease was again reported by Jancke in 1941²⁵ and 1942,²⁶ his description of the disease being identical with that of the authors just mentioned. He noted, however, that the course of the disease might vary and that in some patients the conjunctival and inflammatory symptoms might be slight. Jancke raised the question whether the condition in this epidemic was a recurrence of the nummular keratitis described by Dimmer, Salzmann, Aust and Jese. He admitted that at first glance the differences in the clinical course of the disease would unhesitatingly justify a negative answer to such a proposition. Nevertheless, on account of the various gradations of disease in different persons and the known fact that diseases and contagious disorders of epidemic character varied in their clinical manifestations in different localities and in different periods, he concluded that the disease in this epidemic and all the various conditions reported as keratitis nummularis Dimmer were one and the same disease, and he suggested for the epidemic type the term "keratoconjunctivitis nummularis epidemica." In a discussion of the etiology of the disease, he concluded that it was due to a virus infection. In his second paper, he emphasized

21 Schneider, R. Epidemic of Keratoconjunctivitis in Munich and Surroundings, *Munchen med Wchnschr* **85** 1981-1983, 1938.

22 Meissner, W. Epidemic of Nummular Keratitis (Dimmer) in Bavaria, *Munchen med Wchnschr* **85** 1939-1940, 1938.

23 Senger, W. Studies on a Conjunctival Disease of Unknown Etiology, *Munchen med Wchnschr* **85** 1810, 1938.

24 Schwitalla, H. Epidemic of Keratoconjunctivitis Nummularis (Dimmer), *Klin Monatsbl f Augenh* **102** 491-500, 1939.

25 Jancke, G. Clinical Aspects, Etiology and Therapy of Keratoconjunctivitis Nummularis Epidemica, *Arch f Ophth* **144** 170-181, 1941.

26 Jancke, G. Identity of Keratoconjunctivitis Nummularis Epidemica and Disease Described from 1889 to 1941 Under Various Names (Keratitis Punctata, Nummularis, Maculosa, Epidemica, etc.), *Klin Monatsbl f Augenh* **108** 39-51, 1942.

the uniformity of various epidemic corneal-conjunctival inflammations and pointed out that the cases described by Fuchs, von Reuss and Adler actually constituted a mild epidemic, that Salzmann and Aust really reported a second epidemic and that the 1938-1940 outbreak was in truth only another epidemic of the same disease. He stated the belief that the cases reported from India in 1901 and 1920 and from Batavia in 1912 and 1938 were still other outbreaks of the same disease. He detailed the points of similarity of these various outbreaks and emphasized that all the various reports demonstrated the morphologic similarity of the corneal infiltrates, which he regarded as the salient symptom of the disease. The differences reported by other authors he regarded as unimportant variations of secondary manifestations. A similar review was taken by Hogan and Crawford.²⁷ Their article appeared almost simultaneously with Jancke's papers, and they were unaware of his suggested terminology. However, in their historical review of epidemic keratoconjunctivitis they accepted the view that the earlier cases of "nummular keratitis" were actually epidemic keratoconjunctivitis, and they specifically stated that "epidemic keratoconjunctivitis, keratitis nummularis (Dimmer) Beal's papillary form of conjunctivitis and some forms of keratitis disciformis should be included in one disease entity."

A critical review of the literature which parades under the name of nummular keratitis reveals therefore that the term "nummular keratitis" was coined by von Stellwag and later appropriated by Dimmer to designate what appears to be a quite different disease. Von Stellwag faded from the picture, and the association of Dimmer's name with the term was upheld by Aust and Salzmann. Later, attempts were made to identify this disease with a morphologically similar corneal disease of virus origin and, finally, with epidemic keratoconjunctivitis.

The one pertinent question is whether all the cases described as "nummular keratitis" were manifestations of virus disease of the cornea. This question obviously cannot be answered with any assurance. It is quite probable that the majority of the early cases described as instances of nummular keratitis, especially those with an epidemic tendency, were in truth cases of epidemic keratoconjunctivitis. It is, however, by no means so clear that all the sporadic cases described by Dimmer and other authors were instances of this virus disease.

The argument that some cases of nummular keratitis constitute a separate clinical entity, distinct from epidemic keratoconjunctivitis, would rest on the demonstration of a specific, nonvirus etiologic agent

27 Hogan, M. J., and Crawford, J. W. Epidemic Keratoconjunctivitis (Superficial Punctate Keratitis, Keratitis Subepithelialis, Keratitis Maculosa, Keratitis Nummularis), with a Review of the Literature and a Report of One Hundred and Twenty-Five Cases, *Am J Ophthalm* 25 1059-1078, 1942

for cases which may be characterized as follows. The onset is usually mild, and there is frequently a history of some preceding vague systemic disturbance and minor ocular trauma. The cornea shows superficial infiltrates just below Bowman's membrane. These vary from 1 to 3 mm in size and from two or three up to twenty or more in number. Examination shows that with the slit lamp they are composed of a number of fine, whitish dots. Sometimes the infiltrates are surrounded by a faint halo. Occasionally these subepithelial infiltrates break down and ulcerate, but more often they heal by subepithelial absorption, often leaving depressed facets. Vascularization is inconstant and never a conspicuous feature. Symptoms of keratitis and conjunctival irritation may be present but usually are not marked. The corneal sensitivity is not diminished. There is no involvement of the regional lymph nodes. The disease is apparently not contagious. The course is long and protracted over months or years, often with remissions and exacerbations. The disease tends to be unilateral.

In the last years, 5 such cases have been observed at the Wilmer Institute. In none of these cases had any symptoms suggested a virus infection. The 5 patients all showed evidences of a *Brucella* infection. In experimental animals an almost exact replica of the picture can be produced by infection with *Brucella* organisms. The purpose of this paper is to report these 5 clinical cases and to describe the experimental reproduction of a similar clinical picture.

REPORT OF CASES

CASE 1—A young farmer aged 35 was admitted to the Wilmer Ophthalmological Institute on Feb 8, 1939. His family history was noncontributory, and his past history was essentially without significance. The history of the present illness, as later obtained, was interesting. In January, just prior to the onset of his ocular trouble, he had been caring for a horse with "fistulizing withers," a form of equine Bang's disease. At this time, while treading fodder, he thought dust got in his right eye. He saw his local physician, who apparently removed a foreign body. The eye continued to be moderately inflamed and irritated and had a scratchy sensation, and there was slight photophobia. Examination showed moderate conjunctival and slight pericorneal congestion of the right eye. There were four distinct round infiltrates in the superficial layers of the cornea. On examination with slit lamp, these were seen to consist of a number of fine, whitish dots (fig 1). There was no staining with fluorescein. Cultures of the conjunctival sac showed only a few colonies of *Staphylococcus aureus*. Vision was 20/30, in each eye. Examination revealed otherwise a normal condition. The left eye was normal.

The general medical survey was as follows. The physical examination showed nothing noteworthy except that the patient was slightly undernourished. The search for foci of infection revealed a chronic infection of the right antrum, the teeth and genitourinary tract were normal. Roentgenograms of the chest were normal. Intracutaneous tests with old tuberculin gave a positive reaction only to 0.1 mg. Laboratory studies showed that the blood and urine were normal. The Wassermann reaction of the blood was negative. The patient was then thoroughly

studied for hypersensitivity. He gave negative reactions to all grains, epidermal substances and inhalants. He improved slightly under symptomatic treatment and was discharged from the hospital on February 18.

He returned on May 8, with the story that the eye had continued to be more or less inflamed up to a week before, when it had become worse. Examination showed an increase in the number of subepithelial infiltrates, several of which stained lightly with fluorescein. Just below the center of the cornea was a depressed facet. He was again admitted to the hospital for treatment, and on this admission tests were made for brucellosis. The agglutination test gave a negative reaction, but the opsonocytologic index was high (strongly positive) each cell being packed with *Brucella* organisms. Tests for cutaneous sensitivity to *Brucella* organisms made at this time were invalidated by concurrent fever therapy.

The patient improved under local and systemic arsphenamine therapy and was again discharged. He was seen again three years later, at which time there was still one small nummular infiltrate in the lower part of the cornea. At this time cutaneous sensitivity tests for brucellosis were repeated and gave positive reactions.



Fig 1 (case 1) —Picture taken with the slit lamp, showing nummular infiltrates in the cornea.

CASE 2—A white man aged 23, a farmer, was admitted to the Wilmer Ophthalmological Institute on June 2, 1943, with the complaint of gradually increasing dimness of vision of five weeks' duration. The family history was noncontributory. The significant fact in the past history was a vague illness two years prior to his admission, characterized by vague pains, edema of the ankles and palpitation of the heart. There had been 2 cases of Bang's disease on the farm where the patient had worked in the preceding eighteen months. Five weeks prior to his admission there was dimness of vision in the left eye, followed by inflammation for the last two weeks, but there was no pain. He gave no history of trauma. Examination showed that the right eye was normal throughout. The left eye showed slight pericorneal congestion and three nummular infiltrates, which were slightly elevated, lying beneath Bowman's membrane. One infiltrate either had broken down and epithelized over or had undergone subepithelial absorption, for there was a depressed facet, surrounded by several large vessels (fig 2). The infiltrates were surrounded by a faint, hazy halo. Examination with the slit lamp showed the

usual picture of nummular infiltrates. There was no uveal inflammation. The fundus was normal. Vision was 20/50 in each eye.

The medical survey showed an essentially normal physical condition. There were no apparent foci of infection, the otolaryngologic, genitourinary and dental examinations revealed nothing pathologic. A roentgenogram of the chest was normal. The tuberculin tests all gave negative reactions up to the colossal dose of 10 mg. The blood was normal. Urinalysis revealed nothing abnormal. The reactions to the Wassermann, Frei and Ito tests were all negative. Neutralization tests for *Toxoplasma* gave negative results. The blood chemistry was normal except for a slight elevation of serum globulin (3.2 Gm per hundred cubic centimeters). Cutaneous tests for bacterial sensitivity gave negative reactions except for questionable reactions to beta streptococci. Agglutination tests against both the suis and the abortus strain of *Brucella* gave positive reactions in dilu-

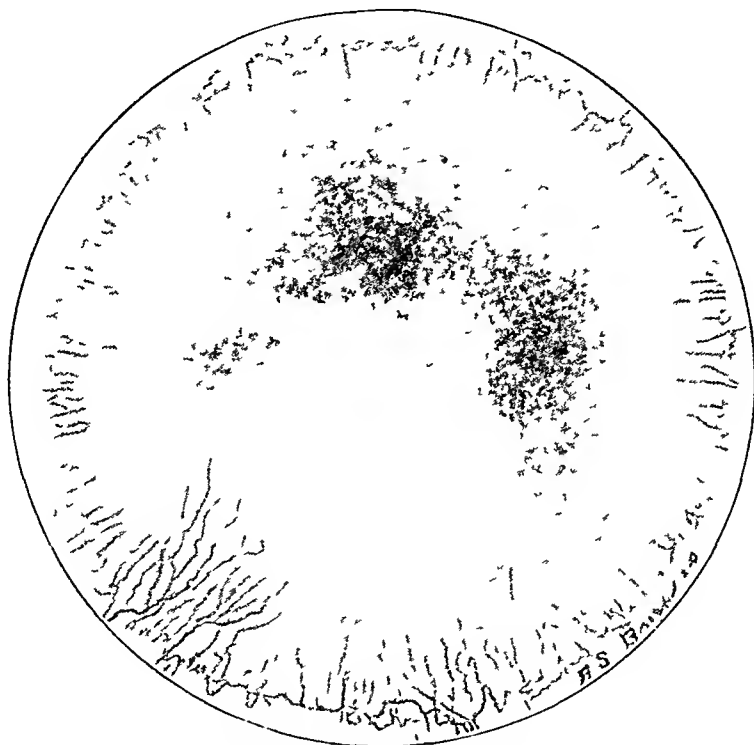


Fig 2 (case 2)—Nummular keratitis with depressed facet and vascularization

tions up to 1:20. The complement fixation reaction for brucellosis was negative. Cutaneous sensitivity reactions for *Brucella* were strongly positive.

The patient was treated with Foshay's sensitized *Brucella* vaccine and showed amazing improvement. He was discharged from the hospital on February 28, with the eye white and the corneal infiltrates much smaller.

CASE 3—A 50 year old white woman was admitted to the hospital on May 22, 1944, with the complaint of a sore, red right eye. The family history was non-contributory. The past history was significant in that she had lived in China for many years and in 1928 had had brucellosis. This was followed by "rheumatism" in the leg and a pelvic disturbance, for which a hysterectomy had been done in 1937. She had had herpes zoster in 1943. The present illness had begun in 1940, when the right eye had become inflamed and painful. This condition had continued, with moderate exacerbations and remissions, up to the time of admission. There was intense photophobia. Examination of the right eye showed low grade ciliary

congestion. There were one small calcified spot in the cornea and several small nummular infiltrates in the superficial parenchyma, which on examination with the slit lamp were found to consist of myriad whitish dots. There was a faint halo around the infiltrates (fig 3). The corneal sensitivity appeared slightly diminished. The epithelium took a fine, punctate stain over the infiltrates. There was no evidence of active uveal inflammation, but on examination with the slit lamp a few old, crenated deposits of keratitis punctata were seen. The fundus was normal, and vision was 20/40 in each eye. The left eye was normal throughout.

The medical survey showed an essentially normal physical condition. There were no foci of infection in the nose, throat, accessory nasal sinuses or teeth. Gynecologic examination showed a large cystic left ovary. The cellular and chemical constituents of the blood were normal. A roentgenogram of the chest showed an old calcified focus in the left hilus and a thickened pleura over the apex

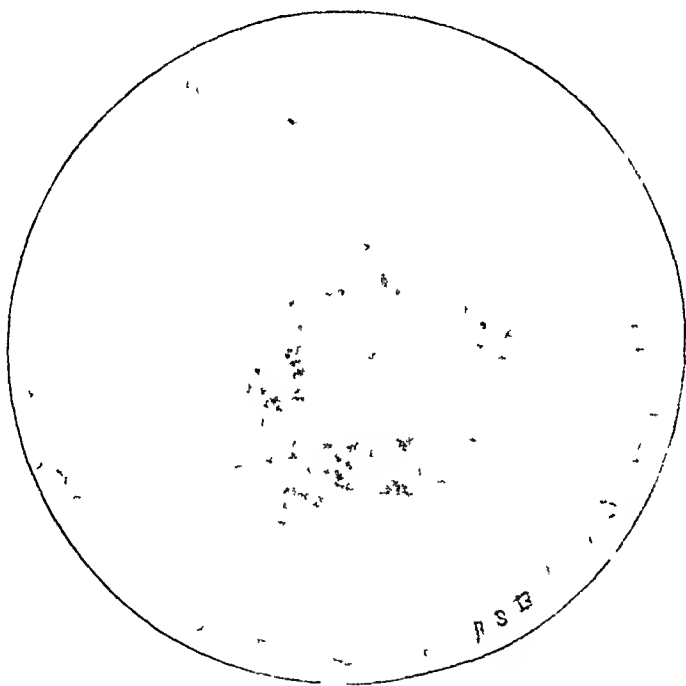


Fig 3 (case 3)—Nummular keratitis with cyst of calcification in the cornea

of the left lung. Intracutaneous tests with old tuberculin showed only a slight reaction to 0.1 mg. The Wassermann reaction of the blood was negative. The urine was normal. The agglutination test for brucellosis gave a negative reaction. The complement fixation reaction for brucellosis was strongly positive. Reactions to cutaneous sensitivity tests for *Brucella* were violently positive.

The patient was given a prolonged course of treatment with Goshay's sensitized *Brucella* vaccine, the injections being given every second day. The initial dose was 0.1 cc of T-2 the weakest dilution, and the dose was gradually increased up to 9 cc of T-50 (T-100 being the maximum concentration). The nummular infiltrates gradually underwent absorption, the eye cleared, and vision rose to 20/30. On Feb 20, 1945 the eye appeared entirely clear except for the old calcified spot in the cornea.

CASE 4—A white woman aged 34 was admitted to the Wilmer Institute on Jan 30, 1945, with the complaint of recurrent iritis. The family history was non-contributory. The past history was especially interesting. She had had a slight attack of pulmonary tuberculosis in 1943, which had completely healed under sanatorium treatment. In April 1944 she had an acute meningeal infection. This was complicated by an infection of the inner ear, which had left the patient stone deaf. Extensive study at this time failed to reveal any cause for the meningitis, and it was thought that possibly it might be a virus infection. There were some vague ocular symptoms at the time of this illness. Recovery was complete except for the residual deafness. The present illness began in August 1944 with a sudden acute, evanescent iritis, lasting only a few days and clearing without any residua. These attacks were recurrent, affecting first one eye and then the other, and continued up to the time of admission.

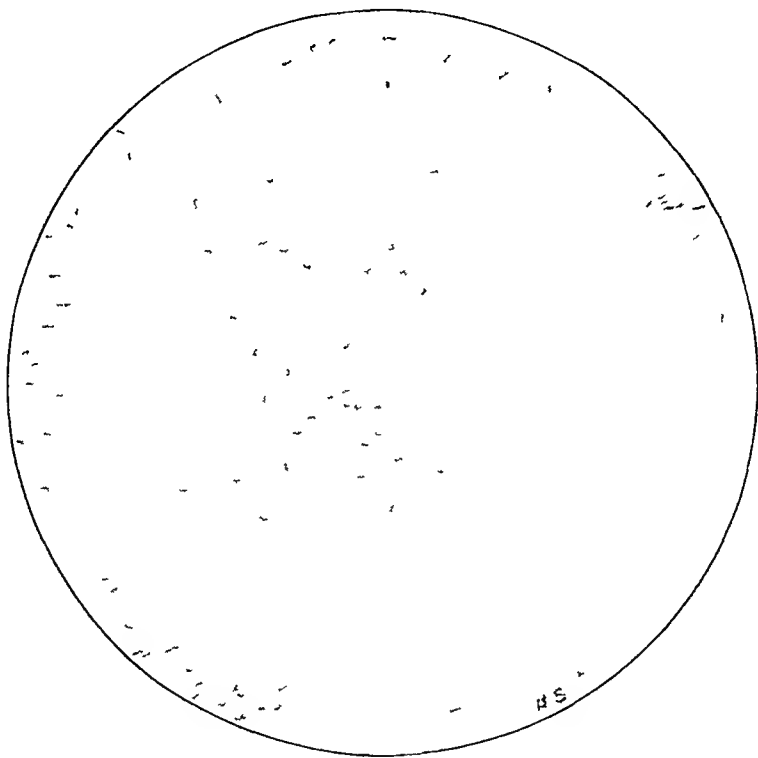


Fig 4 (case 4) —Nummular keratitis complicating recurrent iritis

On admission an attack was just beginning in the right eye, which showed ciliary congestion, a contracted pupil, loss of the normal luster of the iris, blurring of the pattern of the iris, photophobia and lacrimation. Examination with the slit lamp showed a strongly positive aqueous ray but no keratitis punctata deposits and no cells in the aqueous. The fundus was normal, and vision was 20/20. The left eye was normal throughout and remained so during the period of observation. The right eye became more acute on the second day, and on the third day there appeared multiple, small, nummular infiltrates in the superficial cornea (fig 4). Examination with the slit lamp revealed that they were composed of myriad, tiny whitish dots. There was a faint surrounding halo. Corneal sensitivity was normal. The iritis began to subside and on the fifth day had completely cleared. The nummular infiltrates likewise began to clear. The patient was discharged on the fifth day after admission, on completion of the medical study.

The medical survey showed a completely normal physical condition except for the eyes and ears. Otolaryngologic examination showed complete destruction of the inner ear on both sides. Dental and gynecologic examinations revealed nothing significant. Studies of the blood showed a slight secondary anemia. The blood chemistry was normal throughout. A roentgenogram of the chest revealed an old tuberculous lesion, with no activity. Intracutaneous tests showed a moderate sensitivity to 0.01 mg of old tuberculin. Studies for bacterial hypersensitivity showed a moderate reaction to several types of streptococci and pneumococci. Agglutination tests for *Brucella* gave positive reactions in dilutions up to 1:160, the complement fixation reaction was negative, but the cutaneous sensitivity test showed a violent reaction.

This case was especially interesting on account of the differential diagnosis. While the patient had a recent tuberculous infection and showed a moderate

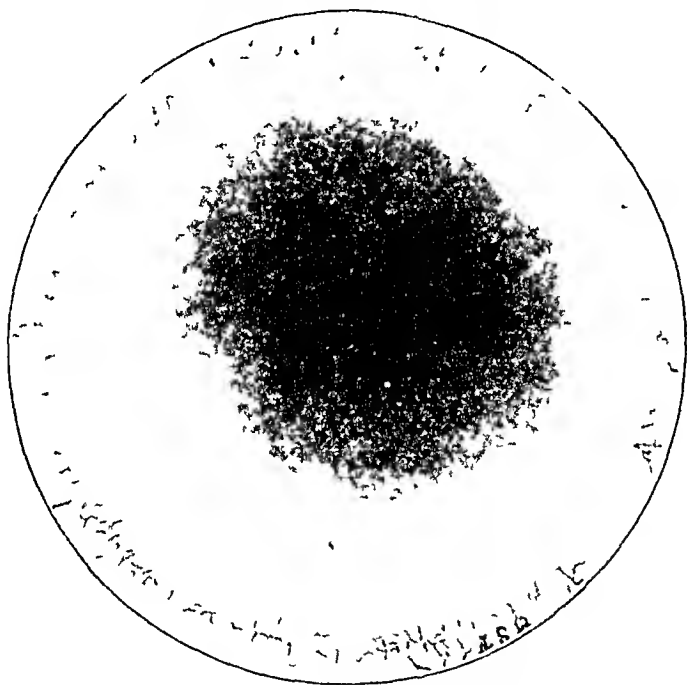


Fig 5 (case 5) —Nummular keratitis

reaction to tuberculin, the iritis was in no way suggestive of tuberculosis, and on a tuberculous basis could only be explained as an allergic reaction to tuberculin, which the patient was not receiving. Certainly, the meningeal infection of 1944 had not been tuberculous. The bacterial hypersensitivity reactions appeared without significance. The outbreak of nummular keratitis in the midst of acute iritis was certainly remarkable. While it could not be proved, it appeared quite probable that the meningeal infection of 1944, which preceded the occurrence of the recurrent iritis, might in fact have been due to infection with *Brucella*. The history of the attack was quite compatible with such a diagnosis.

CASE 5—The patient was not admitted to the Wilmer Institute for study but was seen in consultation with Dr Dorothy Holmes. The *Brucella* studies alone were made in the Wilmer Institute, other examinations being made in Washington, D. C. A full history is therefore not available.

An 18 year old white girl was first seen by Dr Holmes on March 24, 1944. She complained of blurred vision in the right eye. Examination at that time showed multiple nummular infiltrates in the lower part of the cornea just below Bowman's membrane. There were a few large deposits of keratitis punctata. The fundus was normal. Vision was 20/30. The left eye was normal throughout. A complete medical survey, including tuberculin tests, failed to show any cause for the keratitis. On March 31 a cutaneous sensitivity test for *Brucella* was done, which gave a strongly positive reaction. She was given a course of mapharsen, and the keratitis began to improve. By August all but three small infiltrates had disappeared. In January 1945 the eye was clear, and corrected vision had risen to 20/15. At this time, however, similar nummular opacities developed in the left eye (fig 5), and the patient was seen in consultation. The right eye was essentially clear. The left eye showed multiple small nummular infiltrates throughout the cornea. Examination with the slit lamp revealed that these consisted of small, whitish dots and lay just beneath Bowman's membrane. The examination revealed otherwise nothing significant. There were no associated conjunctival symptoms, and corneal sensitivity was normal. Studies for *Brucella* showed a positive reaction to the agglutination test in dilutions up to 1:160, a positive complement fixation reaction and a positive reaction to the cutaneous sensitivity test. The patient was given another course of mapharsen and placed under treatment with Foshay's sensitized vaccine.

An interesting point in this case was that two weeks before the patient was seen in consultation she had been given a cutaneous sensitivity test for *Brucella* which at that time gave a negative reaction but which was followed by the outbreak of keratitis in the left eye. It is an interesting speculation that the cutaneous test may have precipitated the attack in the left eye.

EXPERIMENTAL STUDY

The first observation of keratitis associated with experimental Brucellosis was by Fabian²⁸ in 1912. He reported that 3 of 56 systemically infected guinea pigs showed deep infiltrates in the cornea and lesions in the sclera, choroid and lacrimal gland. No detailed description of the clinical picture or illustrations of the histologic appearance were given, but he stated that "the diseased eyes showed areas of infiltration, chiefly of the lymphoid elements. Some typical tubercles were seen and also intracellular bacilli." In 1928 Orloff²⁹ reported a study of the ocular changes encountered in guinea pigs infected with *Brucella* organisms. The ocular disease occurred in about 10 per cent of the systemically infected pigs. The first manifestations were ciliary injection, followed by the appearance of numerous distinct, small infiltrates in the cornea. Inflammatory changes then occurred in the iris, exudates in the pupillary space and spread of the infection to the other

28 Fabian, M. A Contribution to the Pathogenesis of Br. Abortus Bang, J. M. Research **26** 441-487, 1912.

29 Orloff, K. C. Optic Neuritis and Amaurosis in Malta Fever, Klin. Monatsbl. f. Augenh. **81** 582-591, 1928.

structures of the eye. Histologically, the diseased cornea showed foci of cellular infiltration and new blood vessels, a picture resembling that of syphilitic interstitial keratitis. These eyes finally exhibited iritis, iridocyclitis, chorioiditis, neuroretinitis and cataract. In 1939 Burky, Thompson

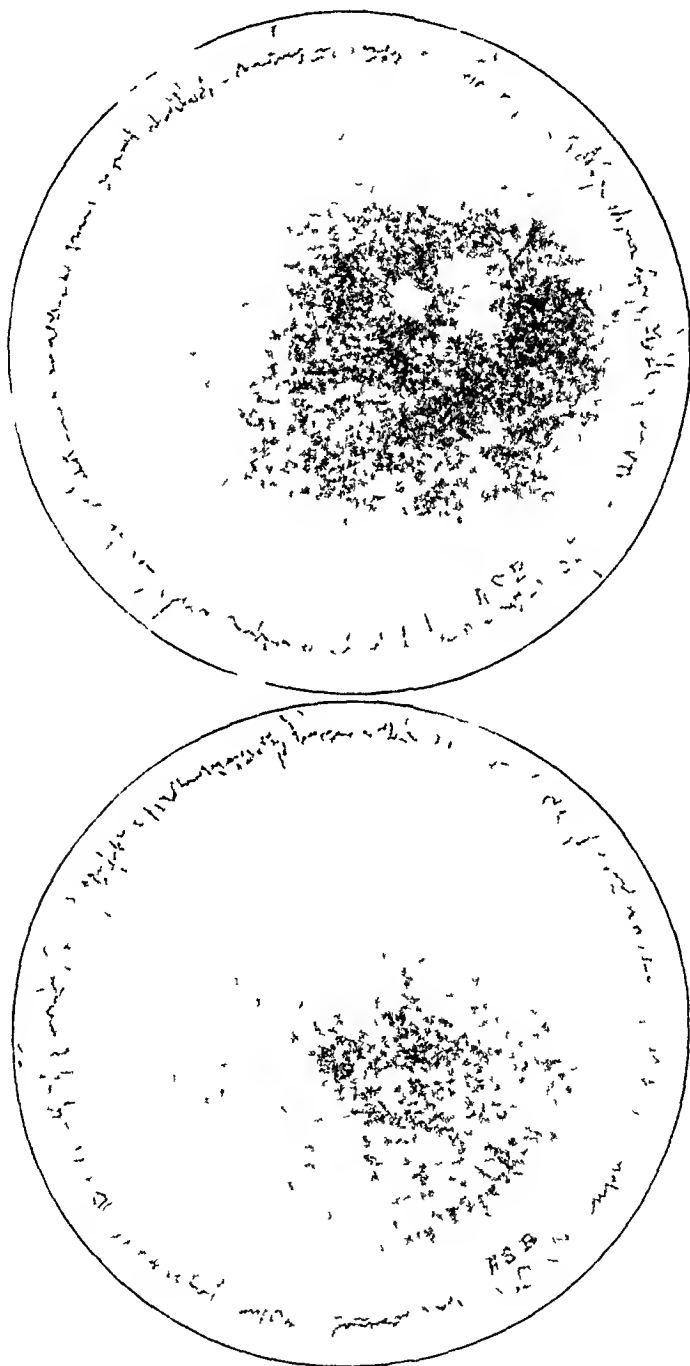


Fig 6—Nummular keratitis in a normal rabbit, produced by light scarification of the cornea with a needle infected with *Brucella* organisms. Four days after scarification.

and Zepp³⁰ reported that 5 of 12 guinea pigs systemically inoculated with brucellosis exhibited ocular lesions. In 5 animals multiple corneal opacities developed. In 2 animals only was there any concomitant iritis, the disease being limited to the cornea in the other 3 pigs. Rabbits systemically infected with *Brucella* organisms have not in our experience at the Institute had ocular complications. However, beautiful multiple infiltrates on the cornea can be produced by slight scarification of the cornea with a needle infected with *Brucella* organisms or by inoculation of the conjunctival sac with 1 drop of a broth culture of *Brucella* organisms after light scarification of the cornea. Figure 6 shows these experimental nummular infiltrates in the normal rabbit four days after the scarification³¹

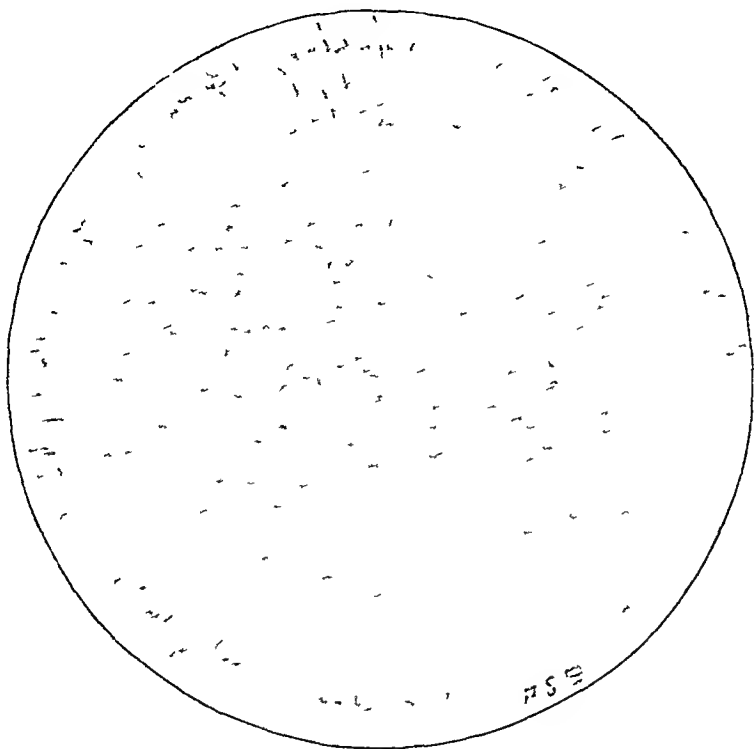


Fig 7—Nummular infiltrates in the cornea of a rabbit infected with brucellosis, produced by secondary scarification with an infected needle. Six days after corneal inoculation.

The course of the keratitis in rabbits thus inoculated varies according to the virulence of the strain of organisms used and the resistance of the rabbits. With virulent strains in some normal rabbits the infection spreads throughout the eye, the corneal infiltrates increase and become confluent, an iridocyclitis with exudates in the anterior chamber occurs.

30 Burky, E. L., Thompson, R. R., and Zepp, H. M. Role of *Brucella* in Human and Animal Ocular Disease with Special Reference to Periodic Ophthalmia in Horses, *Am J Ophth* **22** 1210-1217, 1939.

31 Attempts to photograph these lesions were unsuccessful, the high lights on the cornea masking the nummular infiltrates and confusing the picture.

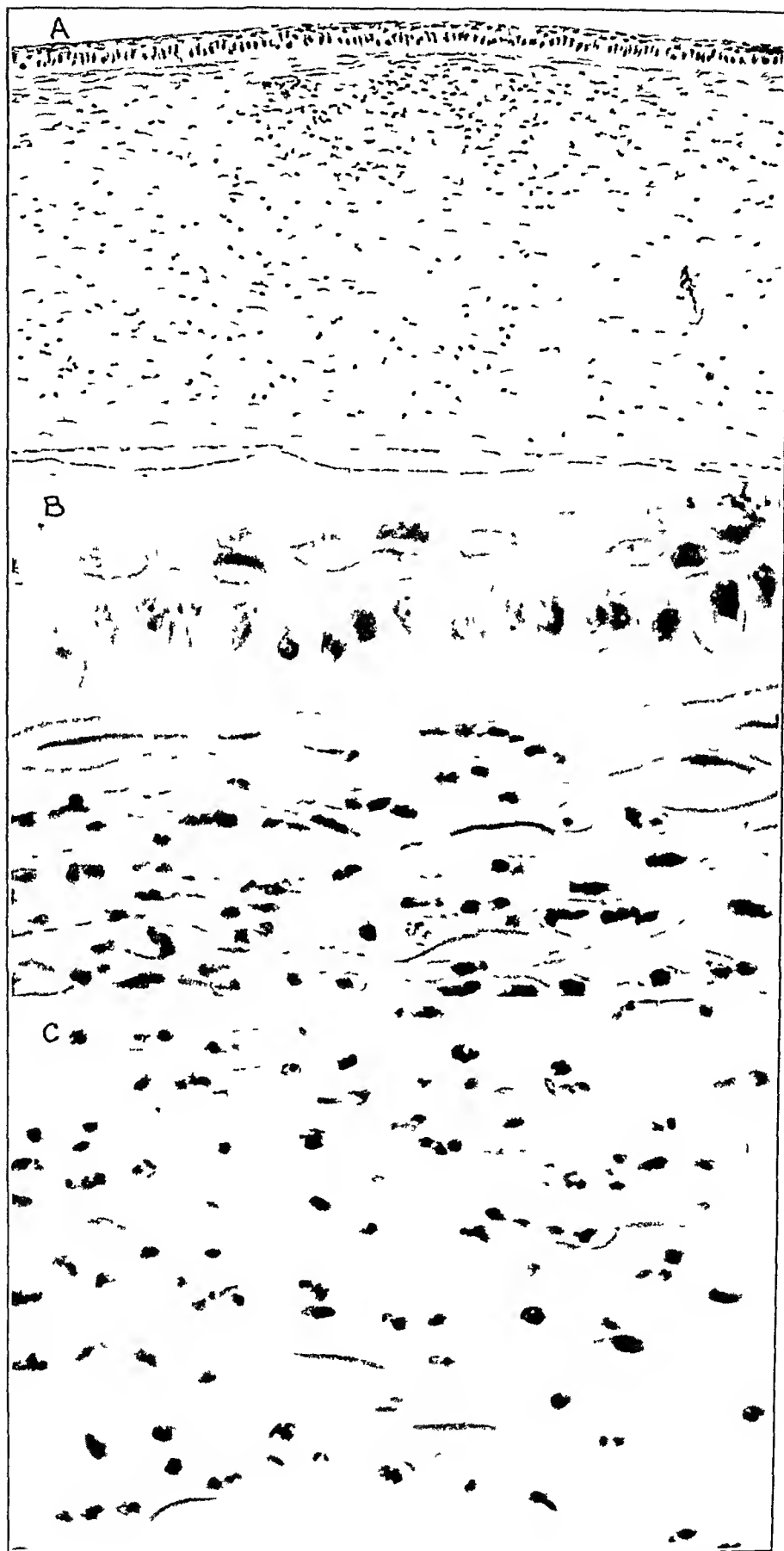


Fig 8—Photomicrographs of a histologic section of the cornea just below the epithelium, showing experimental nummular keratitis produced with *Brucella*
A, low power magnification, *B* and *C*, high power magnification

and the infection spreads to the posterior uvea. These rabbits show no systemic evidences of the disease other than a high agglutination titer. In other rabbits there may be confluence of the primary infiltrates and secondary iritis of varying intensity, followed by a gradual clearing of the eye with moderate corneal scarring and posterior synechias as the residua. In rabbits previously inoculated systemically, and later given corneal inoculations with an attenuated strain of organisms, there may be no confluence of the infiltrates or spread of the infection throughout the eye, the disease remaining limited to the cornea. Figure 7 shows the cornea of such a rabbit six days after the scarification.

Histologic examination of these corneas showed an intact epithelium over the lesions. There were some edema of the anterior uveal stroma and a moderate localized cellular infiltration, chiefly of polymorphonuclear leukocytes, in the anterior portion of the cornea beneath the epithelium. Figure 8 shows photomicrographs of one of these lesions (*A*, taken with the low power lens, and *B* and *C*, with the high power lens). The similarity of these lesions to those produced by herpetic virus is striking.

COMMENT

The 5 cases here reported all have the common denominator of nummular infiltrates of the cornea associated with serologic or allergic evidences of an infection with *Brucella*. The corneal disease in 4 of these cases was quite similar to that in the cases of nummular keratitis previously reported by Dimmer, Aust and Salzmann. Except for the morphologically similar corneal infiltrates, there was nothing in these cases suggestive of epidemic keratoconjunctivitis or other virus disease of the cornea. No other definite etiologic factors were demonstrated in these cases, although in 1 case (1) there was a chronic infection of the antrum and in 2 cases (3 and 4) there were evidences of an old tuberculous infection. The clinical picture in these cases, however, did not suggest either focal infection or tuberculosis as the cause of the corneal disease. An exactly similar corneal lesion can be produced in rabbits by proper inoculation of the cornea with *Brucella* organisms. This, in brief, is the evidence which has prompted the belief that some cases of typical nummular keratitis may in truth be cases of corneal brucellosis. The happy therapeutic result obtained with Dr. Foshay's vaccine in 2 cases strengthens this belief. Equally happy results have been obtained with this vaccine in other cases of chronic ocular brucellosis, and, indeed, in our experience, this appears to be the best treatment in such cases.

It is, of course, realized that virus infections, especially epidemic keratoconjunctivitis, are the most frequent causes of nummular sub-epithelial infiltrates in the cornea and that Jancke, Hogan and Crawford are in the main justified in their view that such cases usually represent

one clinical entity of virus origin. There appears sufficient evidence, however, to separate the cases here reported from such an inclusive classification. If the nummular keratitis in these cases is a manifestation of corneal brucellosis, how should these cases be designated? The demonstration of a probable *Brucella* origin for even a few cases of nummular keratitis is an example of the danger of a morphologic diagnosis, and the term "nummular keratitis," like all morphologic terminology of disease, is a poor one and is likely to lead to endless confusion as different etiologic agents for corneal infiltrates are demonstrated. The association of Dimmer's name with the picture adds to the confusion, for no one knows or ever will know, exactly what condition Dimmer described. Furthermore, he was not the first to use the term. However, since the term "nummular keratitis" is firmly implanted in the literature it would be unwise to attempt totally to abandon it. *Brucella* nummular keratitis would appear to be the happiest term for the condition in such cases as are here reported, since it describes both the etiologic and the morphologic features of the disease.

It is interesting to speculate how the *Brucella* organisms reach the cornea. The frequent history of trauma suggests that the mode of infection may be exogenous. The production of similar lesions in animals by direct infection of the cornea confirms the possibility of such a hypothesis. It would appear probable that these corneal lesions may result from some minor, often unnoticed, trauma and accidental direct inoculation of the eyes. Just what role local hypersensitivity to the *Brucella* organisms may play in the picture is not clear. It is noticeable, however, that in all the cases here reported definite cutaneous hypersensitivity to *Brucella* organisms was shown. The evanescent attacks of iritis shown in case 4 suggest an allergic reaction in the iris, but there is no actual evidence that hypersensitivity plays any role in the corneal lesions.

SUMMARY

The confused literature on nummular keratitis suggests that more than one clinical entity may have been described under this term. Five isolated, sporadic cases are reported, in all of which the classic picture of nummular infiltrates in the cornea and, likewise, serologic or allergic evidences of brucellosis were shown. A typical nummular keratitis can be produced in experimental animals by proper inoculation of the eyes with *Brucella* organisms. From this evidence it seems probable that some of the cases of so-called nummular keratitis reported may actually have been cases of corneal brucellosis. The term *Brucella* nummular keratitis is suggested for the condition in such cases.

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RELATION BETWEEN ILLUMINATION AND VISUAL EFFICIENCY

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THE *British Medical Journal* recently carried an annotation under the title "Conditions for Good Visibility,"¹ based on investigations made by H C Weston at the National Physics Laboratory under the auspices of the Illumination Research Council and published by the Industrial Health Research Board of the Medical Research Council

Weston's investigation was intended to test the value of a method suggested by Beutell² for determining the level of illumination required for the efficient performance of any kind of work involving visual discrimination. The method is based on the proposition that the illumination required for any visual task, as compared with the simplest possible task, depends on certain conditions adversely affecting its performance, that these conditions can be defined and that if the relationship can be ascertained between each of the conditions and the illumination required to compensate for it then the illumination suitable for the performance of the task ought to be capable of actual computation.

Among the more important of the conditions affecting the performance of a visual task are the apparent, or visual, size of the object viewed and the contrast between it and its background or other juxtaposed objects. The effect of size on the illumination required when the contrast is good (black on white) was shown by Weston in 1935,³ and the effect of varying the degree of contrast for different sizes at different levels of illumination, in 1945.⁴

The interrelationship of the variables—size of object, contrast with background and level of illumination—has been studied by several

From the Knapp Memorial Laboratories, Institute of Ophthalmology

1 Conditions for Good Visibility, *Brit M J* **1** 599 (April 28) 1945

2 Beutell, A W. An Analytic Basis for Lighting Code, *Illum Engin* **27** 5, 1934

3 Weston, H C. The Relation Between Illumination and Industrial Efficiency. I. The Effect of Size of Work, Joint Report of the Industrial Health Research Board and the Illumination Research Committee, London, His Majesty's Stationery Office, 1935

4 Weston, H C. The Relation Between Illumination and Visual Efficiency—The Effect of Brightness Contrast, Medical Research Council, Industrial Health Research Board Report no 87, London. His Majesty's Stationery Office, 1945

American investigators, particularly in the decade following World War I. Some measures of performance used have been threshold discrimination (minimum visual angle discriminable), speed of discrimination of detail and speed of reading. The work of Ferree and Rand,⁵ utilizing five sizes of detail (1 to 5.2 minutes of arc) and four contrasts between object and background, both dark on light and light on dark, is most nearly comparable to that of Weston, both as to the range of conditions studied and the measure of performance used. Part of this work was published in the *ARCHIVES* in 1930.⁶ It may be of interest to indicate some points of agreement and disagreement between the studies made by Weston and by Ferree and Rand.

The measure of performance used by Ferree and Rand was the minimum time needed to discriminate the orientation of the gap in a Landolt ring. The test was thus one of static speed of discrimination with the eye already in adjustment. No ocular movements were involved. Time of exposure was controlled by a single exposure rotary tachistoscope. Weston's measure of performance was the speed of cancellation of Landolt rings having a given gap orientation on specially prepared test sheets containing rings having eight orientations. Corrections were made for accuracy and for the action time involved in the mechanical work of cancellation. Results were expressed in terms of average speed of performance per ring. It may be noted that the speeds reported by Weston are considerably lower than those found by Ferree and Rand under similar conditions of level of illumination, size of object and degree of contrast. This is probably because the latter investigators measured directly the shortest exposure time necessary for the discrimination of each test object and no ocular movements were involved. In Weston's work, on the other hand, the eyes were allowed to linger at will over the task, and the measure of performance included both time of discrimination of the test object with the given orientation and the time for the ocular movements made in scanning the rest of the test material. In this respect the task set by Weston is more indicative of actual working conditions which involve movements of the eyes as well as acts of discrimination, that set by Ferree and Rand furnished sensitive experimental means for detecting the factors which influence the eye's power of discrimination and for indicating the trend and direction of their effect. The studies by Ferree and Rand show in all probability the maximum increase of response resulting from increase of

5 Ferree, C. E., and Rand, G. Intensity of Light and Speed of Vision Studied with Special Reference to Industrial Situations. Part I, *Tr. Illum. Engin. Soc.* **22**: 79 (Jan.) 1927, Part II, *ibid.* **23**: 507 (May) 1928.

6 Ferree, C. E., and Rand, G. Size of Objects in Relation to Their Visibility and to the Rating of Vision, *Arch. Ophthalm.* **4**: 37 (July) 1930.

level of illumination, the studies by Weston, the amounts of increase of response produced in ordinary work

Weston's reports are detailed and worthy of study. Among his conclusions are the following:

1 With maximum contrast (black on white) the effect of size is greater at all illuminations than is the effect of illumination at any size. This conclusion can also be drawn from the work of Ferree and Rand.

2 Performance is directly proportional to the logarithm of the size, for sizes from 1 to 4 minutes, but for larger sizes the increment of performance diminishes and is relatively small for sizes from 6 to 10 minutes. The first part of this conclusion can also be drawn from the work of Ferree and Rand. However, for their largest size, 52 minutes, the curve of speed of discrimination does not level off as does Weston's curve of speed of performance but continues in the same proportion as for sizes of from 1 to 4 minutes.

3 The relation between performance and illumination is such that equal logarithmic increments of illumination are accompanied with increments of performance which progressively diminish in value. This was also found by Ferree and Rand. Above 2 foot candles performance becomes practically independent of illumination with sizes larger than 6 minutes.

4 The range of illumination over which performance varies appreciably is different for each condition of contrast and becomes wider as the contrast becomes poorer. However high the illumination is made, performance with a poor contrast can never equal the maximum performance with a good one. In general, for a wide range of illumination the effect of change of contrast on performance is proportionately greater the smaller the size involved. These conclusions were also arrived at by Ferree and Rand.

5 For all sizes, performance varies considerably with brightness difference between object and background, as well as with contrast.⁷ That is, with illuminations necessary to give the same absolute brightness difference between object and background, performance is not the same. It is higher when the contrast is good and the level of illumination low than when the contrast is poor and the level of illumination high. This result was obtained by Ferree and Rand also and was attributed by them to the state of adaptation of the eye and the size of the pupil at the illuminations under consideration.

6 Performance is higher with "reverse" conditions of contrast (light on dark) than with its "normal" counterpart (dark on light). This was

⁷ The formula for brightness difference is $B_1 - B_2$, that for contrast is $\frac{B_1 - B_2}{B_1}$.

also found by Ferree and Rand for the size of test objects used by Weston for the comparison (3 minutes). The result can be attributed, in part at least, to the higher noticeability and greater apparent size of the test object as a whole when presented in "reverse" contrast, due to the phenomenon of irradiation. In this case, irradiation from the white test object causes it to encroach on the black background, thus making it appear larger and more noticeable. In "normal" contrast, on the other hand, the white background encroaches on the black test object, which thus appears smaller and less noticeable. It is true that irradiation tends to diminish the size of the gap in the Landolt ring when the condition is white on black and to widen the gap when the condition is black on white. For this reason, "normal" contrast provides the more favorable situation when the detail is near threshold in value, for example, 1 minute of arc at low illumination, as was found to be the case by Ferree and Rand. But with the supraliminal size of detail which alone was used for this comparison by Weston, the higher noticeability and the larger apparent size of the entire white test letter on the black background are apparently greater factors contributing to speed of performance than is the slight widening of the gap in the black test letter on the white background. The two studies differ in the comparative results obtained at the upper end of the visibility scale. For Weston, performance was more nearly equal under "reverse" and "normal" conditions at high levels of illumination, a result not obtained by Ferree and Rand. The difference in this and in other results when conditions favored high visibility is probably due to the different measures of performance used by the two investigators.

Weston concludes that Beutell's theory is not confirmed insofar as performance is not made independent of contrast when visual tasks differing only in the contrast they present are illuminated so as to present a constant brightness difference. However, if relative performance is considered, i. e., per cent of maximum performance attained with each contrast, a brightness difference which depends on the size of object involved in the task can be found such that relative performance does not vary considerably with contrast. The minimum brightness difference for which this statement is true is that which gives an average relative performance of the order of 85 per cent for all contrasts. It should be mentioned that this statement holds more nearly for visual angles of 4.5 and 1.5 minutes than it does for an angle of 3 minutes—the size which is typical of many practical tasks.

From a practical point of view, Weston's studies and those of Ferree and Rand show that level of illumination cannot compensate entirely for the adverse conditions of small size of detail and poor contrast in

the work, that when the task is such that these factors cannot be improved the level of illumination should be made as high as is compatible with other factors regulating good lighting, such as freedom from high brightness and high brightness ratios in the field of view. In most cases of this type it is likely that the most favorable illumination will be furnished by a good general level of background illumination, free from glare and high brightness ratios, supplemented by local lighting of the immediate task, the source of which must be well shielded from the eyes of the worker.

PHOTOGRAPHY OF THE EXTERNAL EYE

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PHOTOGRAPHIC reproduction of the eye has become an indispensable part of teaching, research and medical records. The mechanical problems involved are different from those found in general macrophotography or microphotography because the eye is neither gross nor microscopic in size. The problems are really those of low power microphotography. Further, because of the problem of blinking particularly in photophobic eyes, the light source should be synchronized with the shutter of the camera and the time of exposure must not exceed a certain minimum. Many types of cameras have been used for this purpose¹. Some are better than others but none solves all the problems that may arise. My associates and I have been working with an apparatus which has been quite satisfactory in our hands and which has some advantages which we believe to be worth while.

APPARATUS

The Leica camera is used in conjunction with a mirror reflex housing which converts it into a single lens reflex camera. This is mounted on an elevating stand, the height of which can be varied through a range of 6 cm. The mirror reflex housing, to which is attached both the lens and the film carrier, is mounted on a rack and pinion, which supplies a fine horizontal focusing adjustment through a range of 2 cm. Coarse focusing is accomplished by sliding the base of the elevating stand on the glass-topped table. A double wire release is used, which raises the mirror of the reflex housing just before it opens the shutter to take the picture. Three of the Leica series of lenses may be used with this setup—the 50, 73 and 90 mm lenses. The shorter the focal length, the greater the magnification obtained. We have used the 73 mm, 1:9 lens as standard, because it gives approximately a 1:1 image size. The reflex housing acts as a bellows extension.

From the Ophthalmological Service of the Mount Sinai Hospital and the Corneal Research Laboratory of the Manhattan Eye, Ear and Throat Hospital.

¹ Bedell, A. J. Colour Photography in Ophthalmology, in Ridley, F., and Sorsby, A. Modern Trends in Ophthalmology, London, Butterworth & Co., Ltd., 1940, pp. 213-223. Bogart, D. W. Clinical Photography with Special Reference to Photography of the Anterior Segment of the Eye, Am J Ophth 25: 62-66 (Jan) 1942. Irvine, R., and Stimson, R. A Method of Ultra Close-Up Photography in Ophthalmology, Arch Ophth 23: 161-163 (Jan) 1940. Knighton, W. S. A Simple Set-Up for External Eye Photography, Am J Ophth 21: 300 (March) 1938.

Our lighting system consists of two 200 watt projection bulbs, which are mounted in aluminum tubes. These are equipped with concave, rhodium-plated mirrors and condensing lenses to direct the light beam, and the projection bulbs are overloaded by 10 volts. The lighting is so arranged that during focusing it is dimmed by a resistance in series with the projection bulbs. (For the resistor, a no. 1 Photoflood bulb has been found to be satisfactory.) When the operator is ready

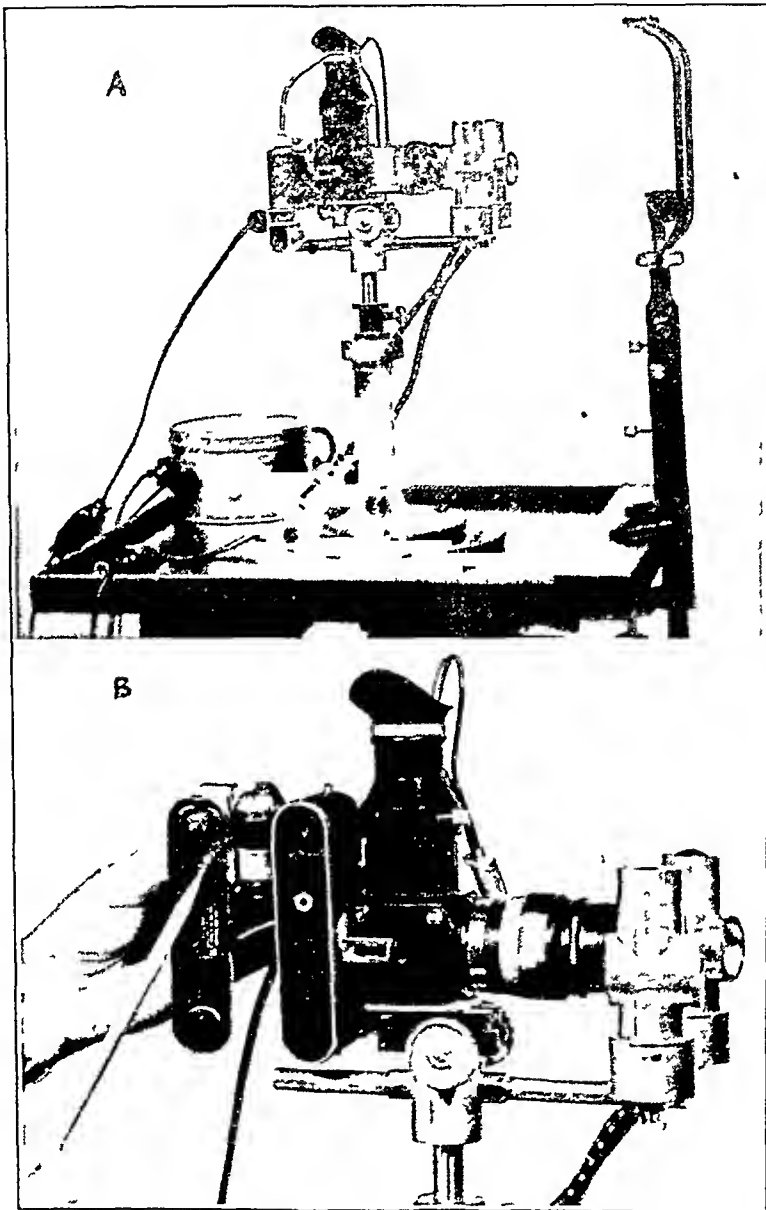


Fig 1—A, the complete apparatus, showing Leica optical system, illuminating system, Micro-Switch bracketed to the base of the film carrier, resistance box and chin rest. B, the camera rotated to the vertical position and the base plate removed and held next the camera. The pencil demonstrates the activating button of the Micro-Switch.

to take his picture, this resistance is shunted, bringing the illumination up to peak intensity. The shunting of the resistance is synchronized with the camera shutter by the use of a Micro-Switch. The Micro-Switch measured only $\frac{5}{8}$ by $\frac{5}{8}$ by $1\frac{7}{8}$ inches (16 by 16 by 478 cm) and has a mechanism so sensitive that

7 ounces (200 Gm) of pressure and a 0.002 inch travel is sufficient to throw it. The contacts will carry up to 1,250 volts alternating current, which is much more than is necessary for our purpose. The switch is bracketed to the Leica base plate in such fashion that the shutter release mechanism throws the switch just before it opens the camera shutter. The net result is that the patient's eye is under observation through the mirror reflex housing under reduced illumination until the instant the picture is to be exposed. Then, by operation of the Leica wire release the mirror is lifted, the illumination is brought up to full intensity and the shutter is snapped.

COMMENT

Film—Since the miniature camera is designed for the use of 35 mm film, and the size of the human eye is such that it fits well, natural size, on this film, this film has been the most convenient type to use. Kodachrome in the 35 mm size is ideal for transparencies, its only disadvantage is that of being somewhat slow. The black and white 35 mm films are available in much faster emulsion speeds and are satisfactory for publication work.

Lenses—Lenses that are used for ordinary photographic purposes are optically corrected for use at infinity and when used at short range are not ideal. A special series of lenses is manufactured that is recommended for low power microphotography. These are the Micro Tessar and the Micro Summar lenses, manufactured by Zeiss, Leitz, and Bausch and Lomb. They are corrected for 1:1 magnification. However, if an ordinary photographic lens is of high quality, it is perfectly satisfactory. So far as the focal length of the lens is concerned, the longer the focal length of the lens, the greater the bellows extension must be to give the same ratio of object size to image size. In other words, using a 50 mm extension on a 50 mm lens or a 73 mm extension on a 73 mm lens will give the same (1:1) magnification, the only difference being that the lens of the longer focal length must be used at a greater distance from the object. This is of practical importance when the illuminating system is to be considered.

Depth of Focus—For any given lens, the depth of focus depends largely on two things: the factor of magnification and the diaphragm stop. Since the magnification is the factor that we choose to keep constant, in order to increase our depth of focus we have to decrease the aperture of the diaphragm. This can be done only when there is sufficient illumination to obtain exposure of the film within the allotted exposure time.

Focusing—Although there are several available means of focusing, we feel that there is only one which is entirely satisfactory. Sliding or folding ground glass screens have the disadvantage that the patient may move or the camera may be jarred out of place before the picture

is taken. Fixed focusing devices of various kinds do not allow much flexibility, and, since the depth of focus is only about 3 mm, it is easy to get a blurred image. By far the best focusing system is the single lens reflex camera. With this the patient can be observed until the time the picture is taken. The mirror reflex housing converts the Leica camera into a single lens reflex camera.

Lighting—The type of light source to be used poses the greatest number of problems. The color temperature must be suitable for Kodachrome, the illumination must be evenly distributed to give flat lighting, the highlight of the cornea must be as small as possible and so placed that it does not obscure the pathologic features. The amount of illumination must be adequate to allow an exposure time of less than one-tenth second because of blinking. Photoflood lamps have the proper color temperature but are large and the light output decreases

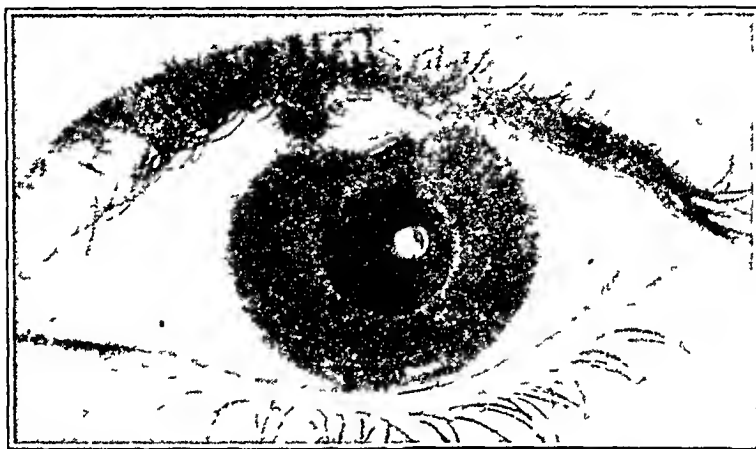


Fig 2—Photograph of corneal transplant taken with the camera

as they burn down. Photoflash bulbs have the disadvantage that a subsidiary source of illumination is necessary for focusing and the exact location of the corneal highlight is not known. Both Photoflood and Photoflash bulbs produce rather large corneal highlights. Projection bulbs are small (1 inch [2.5 cm] diameter), and the concentration of the filament into a small area makes it possible to focus the light beam. These bulbs do not have the required color temperature, but by using a bulb rated for 100 volts on a 110 volt line the color temperature is raised sufficiently for our purpose.

Another type of light source is the gas discharge tube, developed by Edgerton for high speed macrophotography. In this type a high voltage charge is built up in condensers and discharged through the tube. The amount of illumination and the frequency of discharge can be varied, depending on the amount of current used. This method produces excellent photographs, particularly when higher magnification

is necessary. The equipment is expensive and is still in the process of development. It has been used by Gartner² and by Kruse³.

The light sources have to be placed in such a position that the camera does not throw a shadow on the eye, and for that reason a certain minimum working distance must exist between the camera lens and the eye. This is worked out in the choice of the focal length of the lens.

SUMMARY

A camera for photography of the external eye is described, including devices for focusing, illumination and synchronizing the light. My associates and I have been using this device for three years, with good results.

1148 Fifth Avenue

2 Gartner, S. Blood Vessels of the Conjunctiva. Studies with High Speed Macrophotography, *Arch. Ophthalm.* 32:464-476 (Dec.) 1944.

3 Kruse, H. D. Personal communication to the author.

METHOD FOR BIOMICROSCOPIC STUDY OF THE CONJUNCTIVAL BLOOD VESSELS

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THE conjunctival vessels are readily available for study and provide the ophthalmologist with a unique opportunity to learn many of the details of the ocular circulation. Through these vessels pass the blood for metabolic activities of the eye. In addition, the veins drain the aqueous and have a part to play in the complex control of the intra-ocular tension. There are many details of their circulation that can be studied when a proper method is provided.

I¹ recently published a study containing macrophotographs of the conjunctival blood vessels taken with a high speed light with a new ocular camera, made by the Fairchild Instrument and Camera Company, New York. So much was revealed by these photographs that an attempt was made to study the vessels directly at comparable magnifications in the living patient.

The conjunctival blood vessels can be examined in some detail with the usual slit lamp. However, even with the widest slit there is insufficient light, and much is lost. The slit beam is of little advantage in studying the conjunctival vessels. So much has been written of recent years concerning the value of the sharply focused slit beam of light that it seems to be going backward to remove the slit. However, conditions in the conjunctiva are very different from those in the pupillary zone. In the transparent media of the eye, the narrow focused slit beam of light is a splendid arrangement, while its illumination is near the upper limit of tolerance for most patients. However, on the conjunctiva a wider field of illumination is advantageous, and higher intensities of light are easily tolerated. With the combination of more light and a larger field, much more becomes visible through the binocular microscope.

Examination with the modified slit lamp supplements the method of photographic study. The camera yields a permanent record, and with serial photographs the small and rapid changes that occur in the blood vessels can be measured. The modified slit lamp offers a superior binocular view with stereopsis in the colors of the living tissues. The

From the ophthalmologic service of Montefiore Hospital, under a special grant from the United Hospital Fund of New York.

1 Gartner, S. Blood Vessels of the Conjunctiva, Arch Ophth 32:464 (Dec) 1944

examination can be continued for long periods, and the movement of the blood can be clearly followed in many vessels

The modification of the slit lamp can be accomplished in a few minutes, at little cost, and the lamp can as readily be reconverted to the conventional form whenever desired. The modification of the two popular models of the Bausch and Lomb instruments will be described. It should not be difficult to make a similar change with other models. The essential idea is to obtain more light by removing the slit mechanism and its housing. If the condenser is attached to the slit mechanism, they are both removed and a new condenser must be provided to focus the beam.

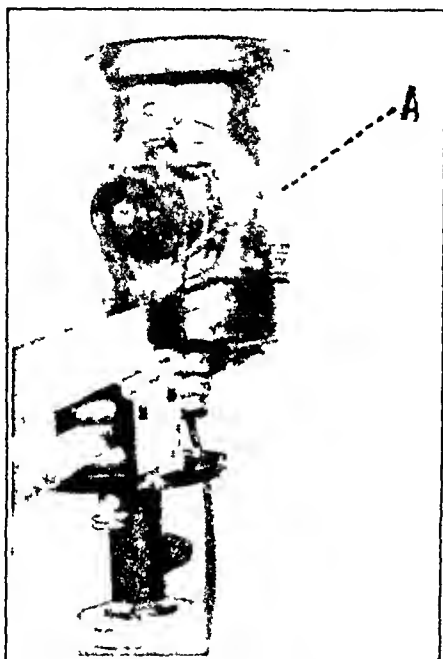


Fig 1—Bausch and Lomb slit lamp. *A*, the screw is loosened and the slit control mechanism removed.

My office model is the type in which the mechanism for controlling the slit is detached by loosening a small finger screw, as shown in figure 1, while the condenser is not disturbed. This permits the passage of a powerful beam of light, the effect of which is further enhanced by slipping out the diaphragm at the focusing lens.

The Simplified Universal model of the Bausch and Lomb slit lamp in use at Montefiore Hospital has the condenser and the slit mechanism combined in one unit. This is removed by loosening the lock screw, shown in figure 2 *I*. A brilliant, broad beam of divergent light appears, for which a condenser is essential. A sufficiently effective one is supplied by the +13 lens in the vulcanite handle, 2 inches (5 cm) wide, of the type usually employed in ophthalmic examinations. This is

attached with adhesive to the light arm, as shown in figure 2 *II*. This simple condenser focuses a powerful beam, which is very hot but is effectively cooled with a 2 inch thickness of plate glass inserted in the line of the beam. Any other type of glass or water cooler would be useful.

Reflections from the condenser and cooler into the eyes of the examiner are avoided by enclosing them in a tube of thick black paper, which is simply wound around them and conveniently attached, as shown in figure 2 *III*.

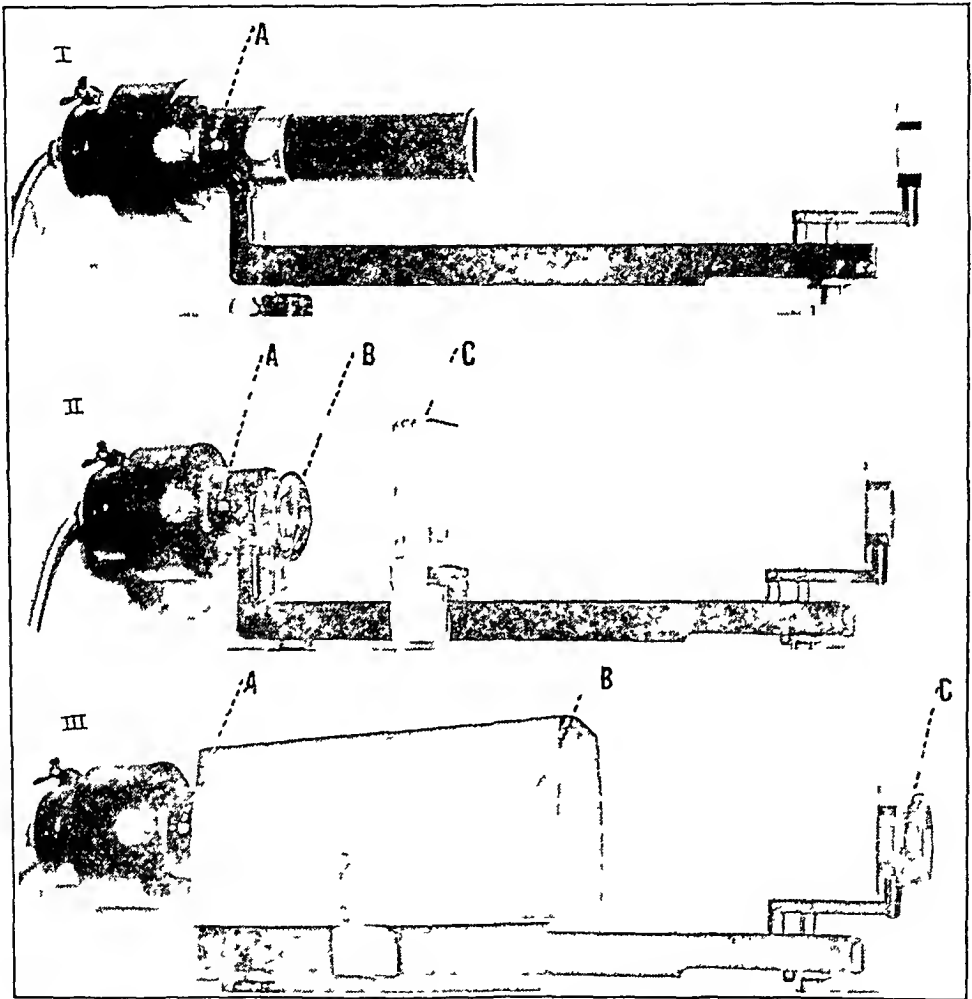


Fig 2—I, Bausch and Lomb slit lamp *A*, the screw is loosened and the housing containing the condenser and slit control mechanism removed. II, lamp after removal of housing containing the condenser and slit control mechanism *A*, screw, which was loosened, *B*, condenser lens 2 inches in diameter, *C*, plate glass, 2 inches thick, for cooling the light. III, lamp after modification *A*, screw, which was loosened, *B*, black paper cover over condenser and cooler, *C*, filter attached to focusing light.

Focusing is accomplished by shifting the light arm and adjusting the focusing lens in the usual way. The smallest circle of light obtained measures 6 mm in diameter and is many times as bright as the best

the scleral conjunctiva, enough light penetrates the ocular coats to disturb some patients. For these persons, the intensity can be diminished by shifting the light arm away from the eye, at the same time providing a larger area of illumination.

A green filter placed in the beam of light is valuable in many examinations (fig 2 III). This diminishes the illumination to a comfortable level for both patient and physician. With the green light, the red blood cells appear black, affording a striking contrast to the white sclera. A good quality of photographic filter should be obtained for this.

The conjunctiva is viewed through the binocular microscope in the usual way, the tarsal conjunctiva and the lids, as well as other parts of the body, can be examined with this instrument in a similar manner. The patient experiences little or no annoyance from this light, which in every way appears innocuous and safe to employ.

Magnifications of 22 to 35 are the most practical in studying the blood vessels. While it is possible to magnify the field over 100 times, the normal oscillations of the eye disturb these views.

There is considerable variation in the appearance of the conjunctival blood vessels with an increase in illumination and magnification. Direct examination of the eye with ordinary light shows a white sclera with delicate blood vessels. With the usual slit lamp more detail of the vessels is seen. With the modified slit lamp many more vessels are seen and a beautiful picture of the circulation is revealed. The photograph obtained with the high speed light and ocular camera, illustrated in figure 3, shows considerable detail of the vessels, but this only suggests the fine view obtained with the modified slit lamp, through which much more is seen.

The conjunctiva is almost transparent, particularly in older persons, so that the blood vessels are easily seen. The red vessels are arranged in a thin layer against a contrasting white background. The walls of most of these vessels are so thin that they are barely discernible, whereas the blood cells circulating in them are visible. There is a conspicuous variation in many features of the circulation from vessel to vessel. In some there is a swift current, which flows evenly, in others the blood moves slowly and irregularly, and in still others the flow may even stop and reverse. In a few instances a pulsating movement synchronous with the heart beat is observed. In some vessels there is a rushing and swirling of a turbulent stream. The aqueous veins, which were so named by Ascher² because of their high aqueous content, are readily identified, and their course is easily traced. Delicate lymph channels can be identified in a few instances.

2 Ascher, K. W. The Aqueous Veins, *Am J Ophth* 25: 1174 and 1301, 1942.

The circulation of the blood has been studied in living animals, birds and reptiles, using such favorable areas as the webs between the toes, the nictitating membrane and the mesentery. In man, extensive studies have been made of the capillaries of the nail bed. The method I have described offers the conjunctiva as the best tissue in living man to study the circulation of the blood in the small vessels. This should

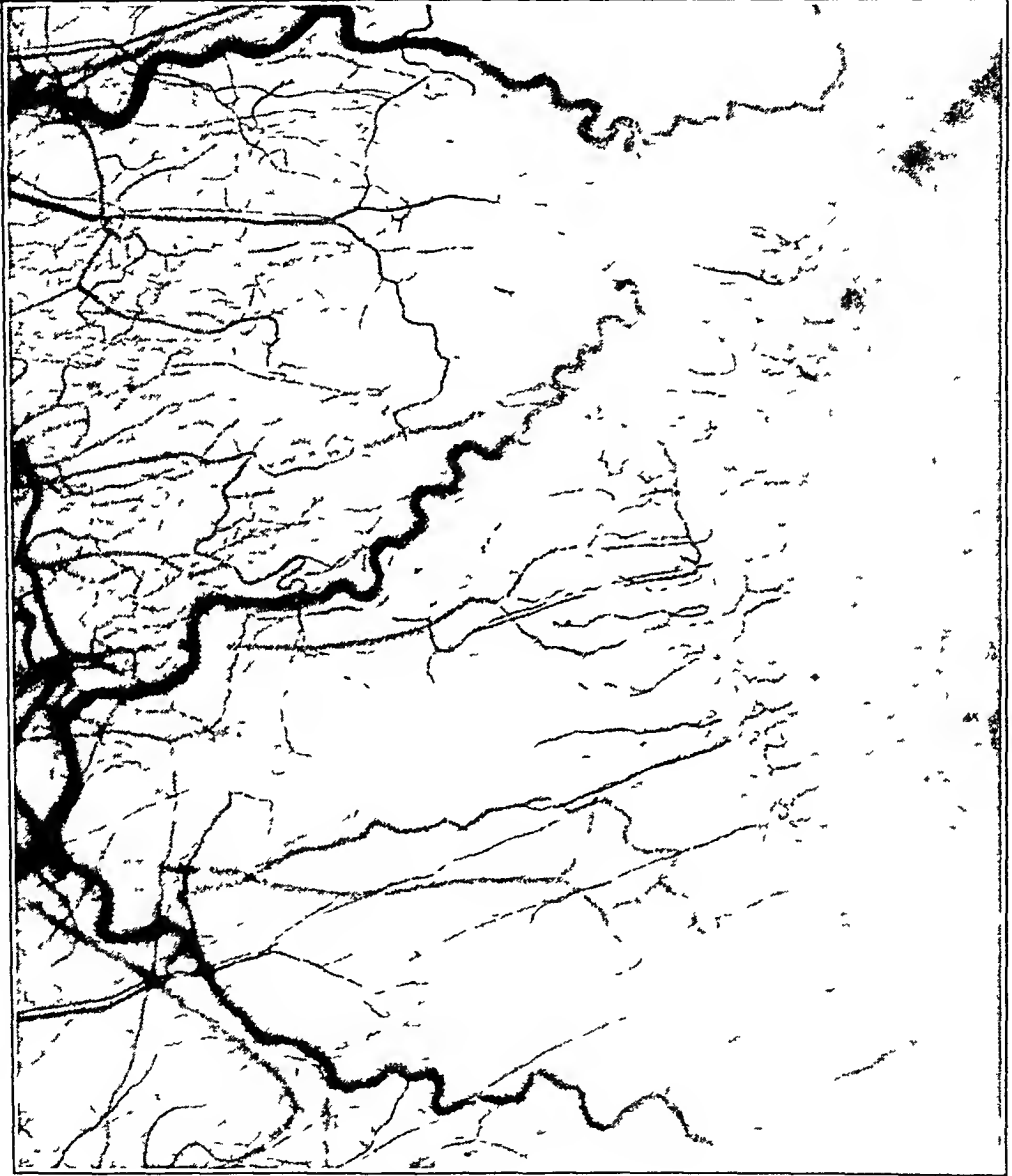


Fig 3—Blood vessels of the conjunctiva

prove useful to the physiologist as well as to the ophthalmologist. Mechanical, chemical and nervous stimulation causes changes in the circulation that can be readily observed and photographed, so experimental studies can be readily performed. Obviously, the integrity of the eye must be respected in any procedure.

SUMMARY

A modification of the slit lamp microscope is presented which considerably improves the ability to examine the finer features of the blood and lymph vessels of the conjunctiva in the living patient

The vessels are so clearly revealed with this improved light that the circulation in them can be easily studied

With this method the conjunctiva is the best tissue in man in which to study the circulation in the small vessels during life

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TECHNICAL USES OF AIR IN OPHTHALMOLOGY

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AND

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THE uses of air in ophthalmology are for the most part limited to the mechanical displacement of tissues. The use of air in various procedures has become more prevalent during recent years.

ROENTGENOGRAPHY

Employing a technic similar to that originally described by Gasteiger and Grauer¹ in 1929, and also discussed by Spackman² in 1932, in which they injected air into the fascia bulbi (Tenon's capsule) immediately next to the sclera, Pfeiffer³ has found the procedure useful in determining whether a foreign body is deep in the eye or just behind it. The air is injected into the potential space between the fascia bulbi and the sclera, and then roentgenograms are taken to show the exact location of the sclera in relation to any opaque foreign body or other radiopaque substance or structure. A summary of his technic follows.

With the eye anesthetized with several drops of tetracaine and procaine, the needle of a 5 cc syringe, with the barrel open, is introduced through the conjunctiva at 4 30 o'clock 8 mm from the limbus, and the point is carried through to come into contact with the sclera of the eyeball. The syringe is then closed gently, thus inflating the potential space which exists around the posterior segment of the eye.

The patient lies on a table, with the head in the lateral position on the cassette and with the injured eye down, and is instructed to direct his gaze in such a fashion as to bring the foreign body, which has previously been localized, in the most posterior position, so that the primary pencil of roentgen rays passes tangential to the point where the foreign body is known to lie. The posterior

Read at the Eighty-First Annual Meeting of the American Ophthalmological Society, Hot Springs, Va., Nov. 12, 1945.

1 Gasteiger, H., and Grauer, S. Zur Diagnose der Doppelperforation des Augapfels mit Hilfe von Lufteinblasung in den Tenonschen Raum, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 40 272-278, 1929.

2 Spackman, E. W. X-Ray Diagnosis of Double Perforation of the Eyeball After Injection of Air into the Space of Tenon, *Am. J. Ophth.* 15 1007-1012, 1932. Spackman cites Gasteiger and Grauer¹ as suggesting injection of air into Tenon's capsule for diagnosis of location of the foreign body in relation to the sclera.

3 Pfeiffer, R. Personal communication to the authors.

surface of the eyeball is well revealed on the film by the air space, and this allows one to decide whether the fragment is in or out of the eyeball

In cases of fracture the presence of air in the tissues may occasionally be of value in localizing small fissure fractures communicating with the air passages

SURGICAL PROCEDURES

In surgical procedures air has been found of value in several ways

A Injuries in the anterior portion of the eye

1 Perforating injuries of the cornea

(a) Recent injuries

In cases of recent laceration of the cornea with incarceration of iris and/or lens capsule in the wound, mattress corneal sutures are so placed that an air-tight closure of the wound is obtained. The iris and other structures are removed from the wound, and sufficient air may usually be inserted to separate the underlying structures from the cornea until aqueous has been reformed. The air mechanically reforms the anterior chamber immediately in approximately normal fashion. The air bubble gradually disappears and is replaced by the aqueous, so that at the end of from three to six days the bubble is entirely gone. The wound in the cornea must, of course, be accurately closed to retain the air bubble, and the patient's head must be placed in such a position that the air bubble will rise to insert itself behind the cornea in the region of the laceration or to separate the structures, which would otherwise tend to become adherent to the posterior corneal surface or be incarcerated in the wound if the anterior chamber remained flat.

(b) Anterior synechias occurring after injuries or perforating ulcers

In cases of anterior synechias to the cornea following late after a laceration, perforating ulcer or incision in the cornea, with loss of aqueous in the anterior chamber, the simple incision of the band frequently results in at least partial recurrence of the adhesions because the raw surfaces made by the incision of the band remain in contact. The adhesions often completely or partially reform unless some means is provided to keep them apart. Saline solution is used for this purpose but is not without danger. I know of at least 1 case of loss of the eye following this procedure. Air forms the ideal substance for this purpose, as it is gradually absorbed, does not dilute the fluids of the eye and produces minimal local tissue changes in the cornea and iris.

In several cases of this condition operation has been performed with success and with no tendency for the adhesions to reform. A special knife has been constructed, similar to the goniotomy knife (fig 1 *A* and *B*), but with a longer blade, with which it is possible to aspirate the aqueous and insert as much air as is required without removing

the knife from the anterior chamber. The injection of the air serves mechanically to put the adhesions on the stretch so that they are more easily severed. If additional air can be introduced in order to keep the lens from coming forward and being injured at the time of incision of the synechias, the danger of traumatic cataract and its sequelae will be reduced.

2 Anterior synechias after discission

Frequently, after discission of a secondary membrane or after iridotomy, where the instrument enters the vitreous, strands of vitreous (or even lens capsule or iris) may be seen stretched forward to the site of the corneal incision. Also, after cataract extraction, iris, lens

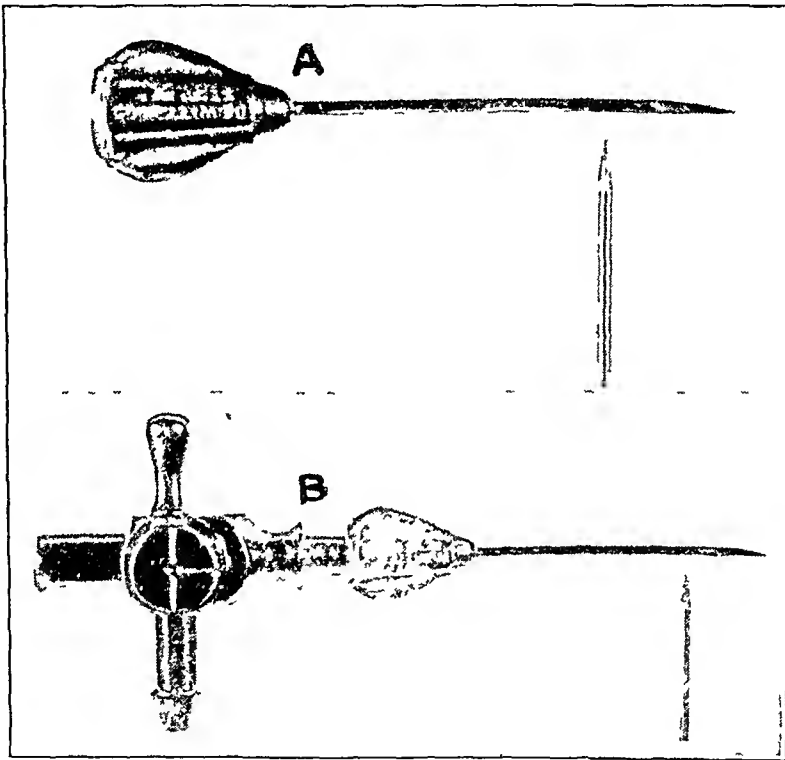


Fig 1—*A*, knife cannula with 5 mm blade and hollow shaft with hole just back of the blade, to which the pointer is directed, *B*, knife cannula mounted on a two way luer connection, ready to have the two syringes attached

capsule or vitreous incarcerated in the wound may cause continued irritation, retraction of the wound, glaucoma or even sympathetic ophthalmia. Simple incision of these strands is frequently ineffective because of reformation of the adhesions. If air is inserted either at the time of the original cataract extraction or the discission or at the time of secondary incision of the anterior adhesions, the structures are separated from the wound in the cornea in the same manner as previously described for lacerations of the cornea. In cases in which these anterior synechias are responsible for secondary glaucoma, the latter may be

relieved simply by easing the traction on them. These adhesions are readily visualized without the use of a contact glass if the aqueous is withdrawn from the anterior chamber and sufficient air injected.

3 Vitreous in contact with cornea

In 2 cases, after intracapsular cataract extraction a mound of vitreous protruded through the pupil and remained in contact with the central portion of the cornea, causing a central corneal haze and, in 1 case, secondary glaucoma. The vitreous was separated from the cornea with a suitably curved iris repositor inserted obliquely at the limbus (vitreo-dialysis) and air inserted to maintain the separation until the aqueous reformed. In both cases the condition was relieved, and in the case with increased tension the intraocular pressure was reduced to normal without any further procedure. The central haze of the cornea which had already developed remained permanently.

4 Cataract extraction

At the end of a cataract extraction, as a final step, injection of air into the anterior chamber helps in preventing incarceration of structures in the wound. An air-tight wound is of course a necessity, and air inserted as a final step aids in separating the underlying structures from the wound, thus preventing complications due to this factor.

When the volume of vitreous is very small, a deep concavity of the cornea is occasionally seen after removal of the lens, with wrinkles in the stroma and usually an intense generalized corneal reaction subsequently. The first reference I have been able to find to injection of air in this situation is one by Elschnig (cited by Selinger⁴). Injection of air helps to restore the normal curvature of the cornea and lessens the postoperative reaction and opacity. This collapse of the cornea usually occurs in feeble or debilitated persons. When the volume of vitreous seems large and tends to push the iris forward into the wound, injected air tends to hold it back. If there has been loss of vitreous during the operation, the insertion of air tends to push the main body of the vitreous back, thus helping to keep it away from the wound. In routine cases the injection of air also helps to reestablish the intraocular pressure, at least in part, thus lessening the danger of hemorrhage immediately after the operation.

The postoperative position of the eye is of course of considerable importance. The eye should be maintained in such a position as to bring the air into the upper part of the anterior chamber, so that it inserts itself behind the corneal wound as nearly as possible. Accurately applied sutures are, of course, a necessity in order to keep the air in the anterior chamber. Selinger,⁴ in 1937, reported the routine use of air in 22 cases

⁴ Selinger, E. Injection of Air into the Anterior Chamber After Cataract Extraction, *Am J Ophth* 20 827-828, 1937 ✓

of cataract extraction (12 of intracapsular and 10 of capsulotomy extraction) In 4 cases extraction was done through a round pupil with no peripheral iridectomy In 1 case of prolapse of the iris the incision was faulty, the iridectomy being done partially with the knife

5 Trephination

As a final step in the performance of a trephine operation for glaucoma, air inserted into the anterior chamber provides a space between the iris-lens diaphragm and the cornea, and some of the air passes out the trephine opening under the conjunctival flap, providing at least a temporary space by separation of the conjunctival flap from the underlying sclera The air is kept in this area by the accurate suture of the conjunctival flap⁵ The air provides at least a temporary space for the filtration of the aqueous and seems to aid in the establishment of permanent filtration This procedure was reported by MacMillan,⁶ in 1939

6 Absence of anterior chamber after cataract extraction, trephination or similar operations

In the delayed formation of the anterior chamber following operation for cataract or trephination, air has been injected into the anterior chamber as an aid in its reformation This procedure is original with Dr John M MacLean, and he will discuss this phase of the use of air MacLean's original work was referred to by Friedenwald⁷ in discussing MacMillan's⁶ paper on the use of air in trephine operations

7 Air goniotomy

Goniotomy was introduced by Barkan⁸ for cases of deep chamber glaucoma The operation has gained only moderate acceptance because of the difficulty attending the manipulation of the heavy contact glass and the knife at the same time and the limitation in the choice of cases to those in which there is a deep chamber, so that the angle of the chamber may be visualized If some of the aqueous is accidentally released, the technical difficulties of the operation are multiplied

5 If a continuous mattress suture of 00000 surgical gut is used for this purpose, it need not be removed This suture is ideally suited to closure of wounds of this type

6 MacMillan, J A Injection of Air as Factor in Maintaining Filtration After Corneoscleral Trephining in Glaucoma, *Arch Ophth* **22** 968-973 (Dec) 1939 Koster (1902), cited by MacMillan, injects air into the anterior chamber as a therapeutic measure in cases of tuberculous iridocyclitis and keratitis MacMillan suggests injection of air into the anterior chamber in cases of delayed reformation of anterior chamber

7 Friedenwald, J, in discussion on MacMillan⁶

8 Barkan, O New Operation for Chronic Glaucoma Restoration of Physiological Function by Opening Schlemm's Canal Under Direct Magnified Vision, *Am J Ophth* **19** 951-966, 1936

With the technic to be proposed it is possible to perform goniotomy in cases of glaucoma with a shallow anterior chamber, as well as in those with a wide angle. By simply increasing the amount of air in the anterior chamber, the depth of the chamber may be increased.

It was thought that if goniotomy could be performed without the use of the contact glass it would be a contribution to simplification of the procedure. It was demonstrated by animal experimentation that a distinct view (fig 2) of the anterior chamber could be obtained if air was substituted for the aqueous. A fine, very sharp no. 27 hypodermic needle was inserted into the anterior chamber of a rabbit in an oblique direction through the limbus and, entering the sclera subconjunctivally 2 mm distal to the limbus, came into the anterior chamber about 3 mm anterior to this point. The needle, mounted on a tuberculin syringe, was directed to a point slightly peripheral to the margin of the pupil, so that the lens was protected from the point of the needle. The aqueous was withdrawn and the syringe removed from the needle and replaced with a second one, with the plunger drawn back halfway. The iris-lens diaphragm was pushed back by injection of 2 cc of air into the anterior chamber from the collapsed position to one slightly farther back than the normal. The angle of the anterior chamber was distinctly visible, and with a binocular loupe the details were readily identified by direct observation without the use of a contact glass. A photograph was taken which shows the relation of the structures in the angle of the anterior chamber (fig 2).

Further experimentation on rabbits was conducted to determine whether there would be any reaction if too much air were left in the anterior chamber or whether it would make any difference how the syringe used for dilating the anterior chamber was filled. Methods that would ordinarily be available in the operating room were used: 1. Unfiltered room air was employed by simply drawing back the plunger of the syringe. 2. Air was drawn through a sterile cotton ball.⁹ 3. The plunger was withdrawn while a short needle was heated to red heat in the flame of an alcohol lamp, the end of the needle being in the flame. 4. A longer needle was used, so that the air from beyond the flame was drawn through a portion of the needle in the middle heated to a cherry red heat. 5. Air from a vial sterilized by immersion in boiling water for fifteen minutes was used. Experimental injection of air in rabbits has been reported on by von Sallmann⁹ in connection with his work on the intraocular use of air.

There was no noticeable difference in the reaction of the eye or in the rate of absorption of the gas bubble depending on the various

9 von Sallmann, L. Air Insufflation into the Anterior Chamber, *Nat. M. J. China* 17: 6-17, 1931.

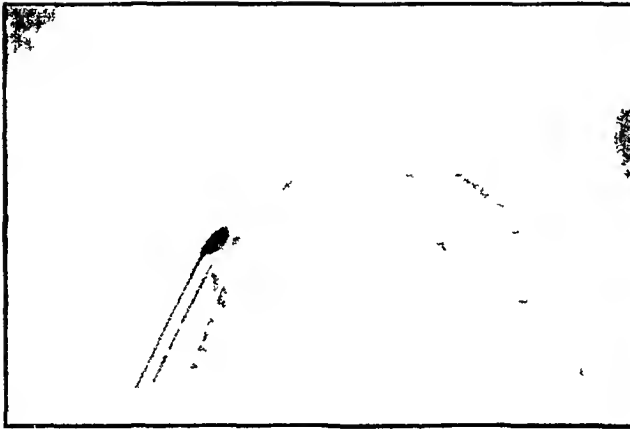


Fig 2—Photograph of the angle of the anterior chamber of the rabbit eye, with air in the anterior chamber and no contact glass. The arrow points to the angle. The color of the lid may be seen through the conjunctiva.

methods of sterilizing the air. In von Sallmann's experiments pure oxygen was found to be more rapidly absorbed.

Some rabbits were subjected to repeated injections of air every two days, the air being kept in the anterior chamber for four weeks to determine whether there was any effect on the eye from prolonged presence of air in the anterior chamber. In cases in which only one injection was made the air bubble in the anterior chamber gradually became smaller and disappeared entirely in an average of four days, at about the same rate as in the human eye.

The feasibility of visualizing the angle of the anterior chamber by means of replacing the aqueous with air prompted the clinical trial of "air goniotomy."

CASE 1—Acute congestive glaucoma of the right eye, iridectomy. Mild chronic simple glaucoma of the left eye, air goniotomy.

Right Eye—Mrs. J. M. had a history of poor vision, pain and redness in the right eye, of one week's duration. Vision was 5/200. Tension was 65 mm. of mercury. The cornea was steamy, the pupil was in mid-dilatation and the disk was cupped. Iridectomy was performed on this eye, with good result, on Feb. 19, 1945. Tension varied from 20 to 40 mm. of mercury (Schiotz). Corrected vision was 20/40 after operation.

Left Eye—The anterior chamber of this eye was not unusually shallow, and with the gonioscope some peripheral anterior synechias were seen in the angle. The tension had been intermittently increased to 35 mm. of mercury, even under the influence of pilocarpine. Vision was 10/200. Goniotomy with injection of air in the anterior chamber was performed, with little postoperative reaction.

Outcome—The tension in each eye has remained normal up to the present time (three months after the operation). The postoperative field of the right eye was slightly contracted nasally, while that of the left eye was normal for a 3/1,000 white test object.

CASE 2—Mr. L. B., aged 38, gave a history of having been struck in the right eye with a brick at the age of 24. The injury left the vision of the right eye slightly less than that of the left. Scars on the retina and a few exudates were found, with vision of 20/25 in the right eye and of 20/15 in the left eye. In April 1944 vision in the right eye became blurred, and a diagnosis of glaucoma of this eye was made.

A 1.5 mm. trephine opening had been made, which was followed by moderately severe iritis and vitreous haze. The tension remained normal for a few months and then rose again to 48 mm. of mercury. The fields were found to be contracted in November 1944. In January 1945, a 2 mm. trephine opening was made, but the operation was not effective in reducing the tension.

On Jan. 30, 1945 a broad-based portion of the iris was removed, this was effective for a few weeks. A broken root of a tooth, about which an area of rarefaction was seen in roentgenograms, was removed in the latter part of February. I saw the patient on March 3.

Vision with correcting lenses was 20/200 in the right eye and 20/13 in the left eye. Tension in the right eye was found to be elevated, measuring 48 mm. of mercury (new Schiotz). There was a surgical coloboma of the iris above with a peripheral iridectomy wound behind a trephination scar in the temporal pillar.

The media were clear, and there was glaucomatous cupping of the nerve head. There were numerous posterior synechias and some organized exudate on the anterior capsule of the lens. Gonioscopic examination revealed numerous peripheral anterior synechias in the angle of the anterior chamber, and at the site of the trephination the ciliary processes were seen to be drawn forward, to close the opening. In the area of the iridectomy the pigment of the ciliary processes was seen to be drawn forward and to spread out over the inner aspect of the cornea at the site of the incision.

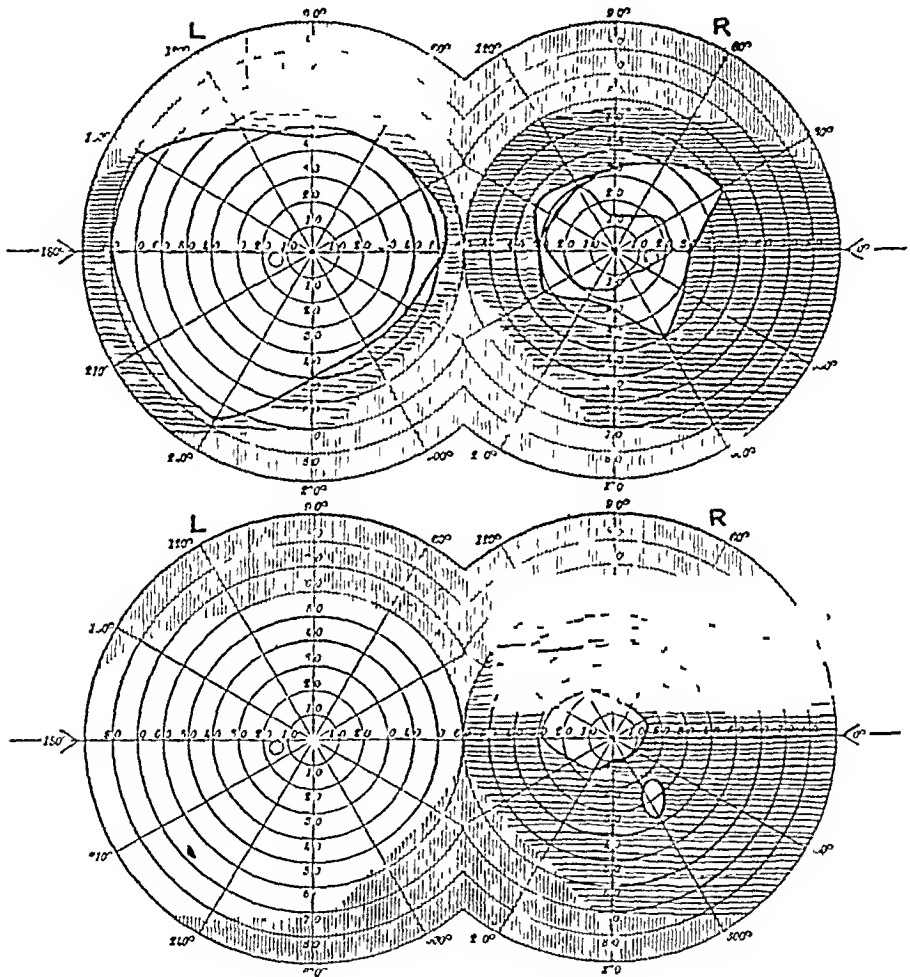


Fig 3 (case 2)—The upper part of the illustration shows fields taken before operation on right eye (left eye 3 mm at 260 mm, right eye (a) field for light and (b) field taken with a 15 mm test object at 260 mm), the lower part of the illustration shows the preoperative central field of the right eye

There was marked contraction of the field of the right eye but no involvement of the field of the left eye (fig 3)

Examination of the left eye revealed nothing pathologic except a few small peripheral anterior synechias across the angle of the anterior chamber at the upper pole, as seen with the gonioscope. Visual acuity and the visual fields were normal, as were the tension and fundi.

Roentgenographic study of the teeth (March 30) showed nothing pathologic. No broken roots or devitalized or unerupted teeth were present.

Air goniotomy was performed on March 31. A no 27 hypodermic needle attached to a tuberculin syringe was passed obliquely into the angle of the anterior chamber, entering the conjunctiva 2 mm back of the limbus at the 9 o'clock position and being directed toward the 6 o'clock position in order to keep the point over the iris. It entered the anterior chamber about 0.5 mm anterior to the plane of the iris. The aqueous was aspirated, and another air-filled syringe was placed on the needle. Air was injected, pushing back the iris-lens diaphragm until the angle was well seen. The peripheral anterior adhesions were cut, and

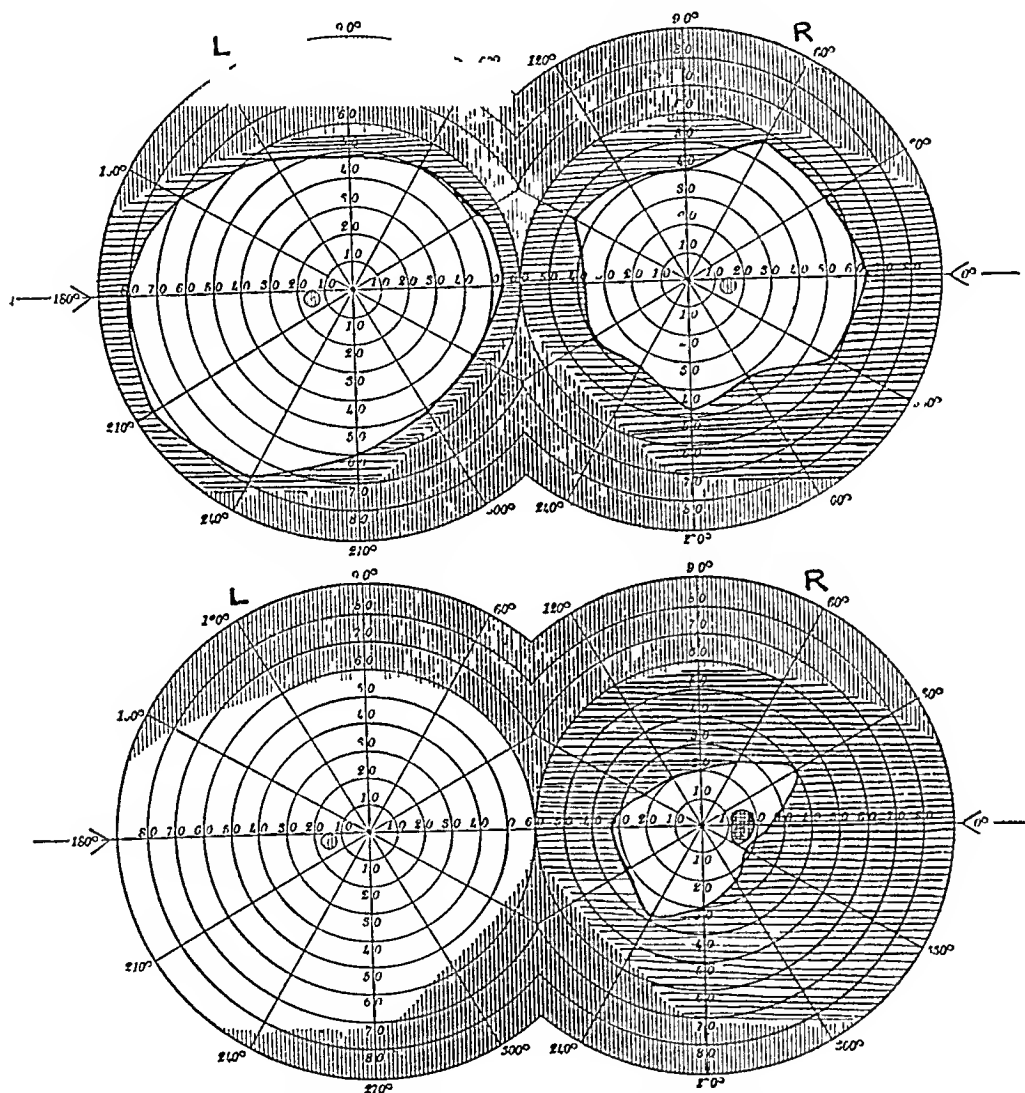


Fig 4 (case 2) —The upper part of the illustration shows fields taken after operation on right eye (left eye 3 mm test object at 260 mm, right eye 20 mm test object at 260 mm), the lower part of the illustration shows the central field of the right eye

an incision was made on the inside of the cornea in the region of Schlemm's canal for about two-thirds the circumference of the anterior chamber. An attempt was also made to scrape back some of the pigment which was blocking the trephine opening above, at 12 o'clock. A drop of physostigmine was instilled and a dressing applied.

There was little postoperative reaction, and the tension was normal during the immediate postoperative course, until April 10, when the patient left for home

The air bubble gradually disappeared and was completely gone at the end of four days. The peripheral limits of the fields had extended. The record of the fields taken on March 9 is shown in figure 4. Vision remained at 20/200 with a —4.00 D sphere.

His oculist has written me that the tension rose one week after his return home but was brought under control with the use of pilocarpine. The final judgment as to the permanence of the result will only be decided by time.^{9a}

CASE 3—Glaucoma of the left eye following cataract extraction

An immature lens was extracted, with loss of vitreous. There were old ruptures of Descemet's membrane in each eye, more pronounced on the right, which were presumed to be due to a birth injury. Vision in the right eye had always been poor, owing to the pathologic condition of the cornea.

A capsulotomy extraction with complete iridectomy had been done on May 18, 1944, and when the patient was seen on April 3, 1945 there was a moderately developed secondary membrane. Vision was 20/50 with correcting lenses. Tension was 20 mm of mercury but became greatly increased by the preoperative nervous tension, so that the cornea became steamy. Combined air goniotomy and dissection was performed. The fibers of organized lens capsule and anterior vitreous condensation layer were incised where they were incarcerated in the wound, and the incision was made on the inside of the cornea near the angle of the anterior chamber.

The membrane was incised centrally with the goniotomy knife as soon as the incision for the goniotomy was completed.

The patient's oculist has informed me that the tension has remained normal during the period since the operation, which at the time of writing is two months.

The feasibility of goniotomy by a simplified technic has been demonstrated. No suggestion as to the permanence of the results is implied by the foregoing reports, as insufficient time has elapsed in any of the cases. This report deals particularly with the simplification of the technic so that more surgeons may be induced to give the operation a trial and a judgment may be made as to the worth of the procedure. The originator of goniotomy, Barkan,⁸ who performed his operations by balancing a contact glass on the eye while manipulating the knife intraocularly underneath it, reported excellent results in cases of wide angle glaucoma and congenital glaucoma. In the 3 cases reported here the operation was at least temporarily successful.

New Instrument—Obviously, a goniotomy knife with a hollow shaft and an opening near the blade would be a development still further simplifying the technic. Such an instrument was designed (fig 5A), with an opening near the heel of the blade.¹⁰ On the other end is attached a two way luer connection. To this are connected a luer lock 2 cc syringe, with the plunger withdrawn part way, and to the side connection another syringe is attached by a small flexible tube (fig 5B). The second syringe is used to withdraw the aqueous, while the first one,

^{9a} There were a return of increased tension and further loss of vision a few months later.

¹⁰ Made for me by H. E. Cullman, 2306 Morris Avenue, New York (53).

with the plunger partially withdrawn, is used to insert the air into the anterior chamber. Sufficient air can be inserted to deepen the anterior chamber so that any peripheral synechias can be easily seen and put on the stretch and incised. An incision into Descemet's membrane on the inside of the chamber angle can be made under direct vision without the use of a contact glass.

8 Therapeutic uses

Koster, in 1902, used air in the anterior chamber as a therapeutic aid in cases of tuberculous iridocyclitis and keratitis. The author has had no experience with this use of air.

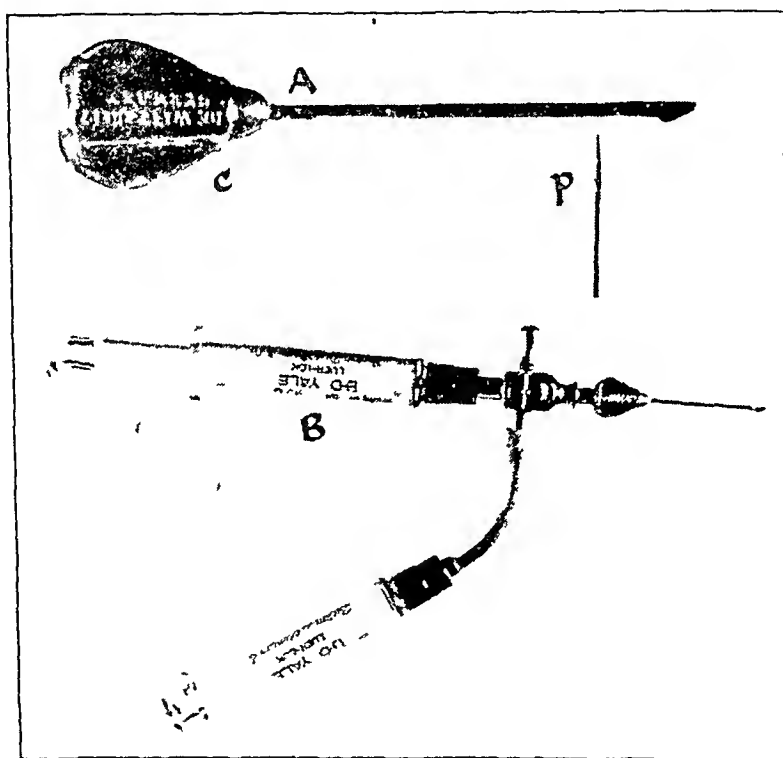


Fig 5—*A*, instrument for air goniotomy with a hollow shaft. *P*, pointer designating small opening in the side of the hollow shaft, *C*, connection for luer tip. *B*, assembled instrument complete with two syringes, one for withdrawing aqueous and the other for inserting air.

B Injuries in the posterior part of the eye

1 Injection of air into the vitreous

In the operation for detachment of the retina, many authors¹¹ have described injection of air into the vitreous with the idea of forcing the

¹¹ Ohm, J. Ueber die Behandlung der Netzhautablosung durch operative Entleerung der subretinalen Flüssigkeit und Einspritzung von Luft in den Glaskörper, *Arch f Ophth* 79.442-450, 1911. Rohmer. Effets des injections d'air sterilise dans le vitré contre le décollement de la rétine, *Arch d'opht* 32 257-274, 1912. Jeandelize, P., and Baudot, R. À propos du traitement chirurgical du

retina against the choroid, thus providing at least a temporary apposition of the retina and the choroid. This should favor the formation of adhesions between the retina and the choroid, with more certainty of the traumatic and thermal chorioretinitis produced forming adhesive bands to hold the retina permanently in close approximation with the choroid. The retina thereby would be more likely to be retained permanently in its proper position.

COMMENT

Many uses suggest themselves for the employment of air, of which the following are suggested:

1. Certain conditions in which direct visualization with the slit lamp would render the angle of the anterior chamber more easily examined, especially when the chamber is shallow, the insertion of air would make the area readily accessible for direct inspection with the slit lamp.

2. In certain cases of glaucoma in which it is desirable to test the lability of the choroid with the possibility of determining the amount of blood in the vascular system of the eye, injection of air would distinguish between a shallow anterior chamber due to an actual increase in the size of the vitreous and lens within the eye and one due to vascular congestion of the choroid. In case of choroidal congestion the injection of air would result in forcing the blood out of the choroid by compression and in restoring to normal, or in increasing the depth of the anterior chamber. The pressure measured on a manometer would serve as a guide, and the volume of air could be measured and the amount used as an index. Once this value has been established, comparison with a normal set of values might form a valuable indication of the type of glaucoma present.

3. The rate of formation of the secondary aqueous could be readily determined simply by aspirating and measuring the amount obtained per minute. In a recent case, that of a young boy with anterior synechias of traumatic origin involving the lens capsule, 2 cc of aqueous was withdrawn in the course of three minutes. This rate was noted while preparing to sever the anterior synechias by withdrawing the aqueous prior to injection of air in an attempt to deepen the anterior chamber and so to simplify the incision of the anterior synechias.

It is interesting to speculate on the diagnostic and therapeutic use of various gases that might be used to detect or combat bacterial growth or

decollement spontané de la rétine, *ibid* 43 413-414, 1926. Rohmer (1912) and Ohm (1911), cited by Jeandelize and Baudot. Anderson, J. R. *Detachment of the Retina*, London, Cambridge University Press, 1931, pp 163-165. Arruga, H. *Decollement retinien. L'urgence opératoire, l'injection d'air, les grandes desmersiones*, Bull et mem Soc franç d'ophth 49 288-303, 1936. Rosengren, B. *Ueber die Behandlung der Netzhautablösung mittelst Diathermie und Luftinjektion in den Glaskörper*, Acta ophth 16 3-42, 1938. Spaeth, E. B. *Principles and Practice of Ophthalmic Surgery*, ed 2, Philadelphia, Lea & Febiger, 1941, p 822.

otherwise affect abnormal intraocular conditions, but these suggestions must of course await further investigation

CONCLUSION

Injection of air is a valuable mechanical aid in many routine operations and renders easy certain procedures which would otherwise be very difficult and makes others safer by restoring the tissues immediately to a more normal position. Further uses for air and other gases will, undoubtedly, be developed as time goes on. Troncoso's development of the use of the gas from a magnesium implant in cyclodialysis is an example.

DISCUSSION

DR J. GORDON COLE, New York. Experiments on rabbits were made in an attempt to answer the following questions: 1. Is it feasible to attempt visualization of the angle of the anterior chamber by the injection of air without the use of contact lens? 2. Where are the histologic effects of air in the anterior chamber? 3. What is the bacterial content of the air to be used for injections into the anterior chamber?

In answer to the first question, experiments proved that the angle of the anterior chamber is distinctly visible by direct observation after injection of air.

In answer to the second question, a number of rabbits received one injection of air into the anterior chamber and the eyes were removed on the sixth day. Microscopic examination showed that there were no pathologic changes. Another series of rabbits received twelve injections, one on alternate days, and after twenty-eight days the eyes were removed and examined. The iris showed atrophy, thickening, adhesions and infiltration with lymphocytes, fibroblasts and plasma cells.

In answer to the third question, the air was passed through a cotton filter, (2) the needle was heated in a flame and (3) the air was drawn through an unheated needle, the contents of the syringe were emptied over a nearly closed blood agar plate, and in another series of experiments the air was mixed with equal amounts of heart-brain broth. After seventy-two hours of incubation there was no growth on the mediums. Dr. Cole concluded that these experiments would justify injection of a limited amount of air into the anterior chamber. The needle used in these experiments was a 27 gage.

DR JOHN MCLEAN, New York. Injection of air into the orbit, particularly within Tenon's capsule, for additional information on the localization of foreign bodies has proved its value without question. Injection of air into the soft tissues of the orbit has been advocated for the better roentgenographic delineation of orbital tumors, and I have tried it in 6 cases. I have been amazed at the amount of air which can be pumped into the soft tissues of the orbit without any apparent ill effects. Of these 6 cases, the tumor proved to be intraorbital in 4, and in 2 cases it was the so-called pseudotumor. I must say however, that in all 6 of these cases the injection of air was of no value whatsoever in helping with the roentgenographic delineation of the lesion.

When one speaks of air in the anterior chamber, there immediately arises the question whether to use air or isotonic solution of sodium

chloride Experience shows that saline solution escapes rapidly, whereas air does not leak nearly as rapidly or as often In a recent textbook on ocular surgery, a paragraph is devoted to the various methods for removal of a bubble of air from the anterior chamber if it should enter accidentally during the cataract extraction, yet Dr Hughes and others have shown that such a bubble is not only harmless but sometimes advantageous

Also not mentioned in the paper are the recent procedures which have been used by Dr T L Terry, of Boston, in the surgical treatment of retrolental fibroplastic disease The method consists in part of ciliary trephining and in part of artificial deepening of the anterior chamber One of Terry's difficulties was in attempting to deepen the chamber with solution of sodium chloride It could be done better with air

Injection of air into the anterior chamber after cataract operation seems to be of no great value if the initial wound is closed sufficiently tight with adequate corneoscleral sutures, for the problem of delayed reformation of the chamber, from which most of the difficulties arise, will be practically eliminated

In a gonioscopic study of eyes after operations for glaucoma it appeared that in cases in which anterior peripheral synechias either were formed for the first time or were extensively increased by the operation the results of injection of air were not so good as in the cases in which such changes in the angle did not take place Therefore it seemed worth while to prevent the postoperative formation of anterior synechias by filling the chamber with air at the time of operation in order to keep the tissues apart, this was done in a series of cases at the time of the external filtering operation After study of the entire series, it became apparent that this precaution was not necessary, that the complication occurred only in cases in which reformation of the chamber was delayed, and that in those occasional cases the complication may be corrected by the postoperative injection of air, when it is decided that the chamber will not reform properly The injection can be made at the limbus, the needle being kept entirely away from the site of the operative incision At about the same time Dr J A MacMillan was injecting air under the flap in trephining operations, and, as he stated, when he did this some of the air usually got into the anterior chamber When I injected air into the anterior chamber, some of it worked up under the flap Anatomically we presumably made about the same injection of air, though one did it for one purpose, and the other for another, and the results were apparently about the same

The injection of air into the vitreous in operations for detachment of the retina has been discussed many times, there again arises the question of the use of air instead of saline solution The main objection is that if enough air is injected to be worth while, the vitreous will seriously interfere with the examination of the fundus in the early postoperative period

The arguments for use of air against that of a saline solution include the fact that air is a gas that it is compressible and elastic and can be introduced under pressure and that it has a springlike action of pressing the retina against the choroid, whereas saline solution, or any other liquid, is incompressible The solution occupies space but exercises no

pressure against the retina to hold it in place. Injections of air in the vitreous has seemed to be particularly useful in cases of detachments in aphakic eyes a condition which used to be considered nearly hopeless. Here its effect has been striking.

To inject air into the anterior chamber of a very soft eye, a track through the cornea can be made with a sharp Ziegler knife or a very narrow Wheeler knife, without losing any fluid, and then a sharp needle is thrust along the same track.

DR LUDWIG VON SALLMANN, New York. Many years ago I became interested in the influence of air in the anterior chamber on the blood-aqueous barrier. In an experimental study, I found that the permeability of this barrier to the small molecule of fluorescein was increased to a much greater degree by an injection of air than by a simple paracentesis. Later it was found that this is also true in regard to large molecules of protein. As Dr. Cole mentioned, the protein content of the aqueous three days after injection of air (200 to 240 mg per hundred cubic centimeters) was two or three times as great as that determined three days after paracentesis (80 mg per hundred cubic centimeters). The effect of this treatment on the permeation of systemically applied antibiotics into the eye has not been studied sufficiently. Application of these results obtained on rabbits to the human eye would indicate that the replacement of a great part of aqueous with air would tend to promote the development of adhesions.

DR MURRAY A. LAST, New York. In 1937 I presented 3 cases in which injection of air into the orbit was helpful in outlining the tumor. The cases were those of a sarcoma, an implantation cyst and a pseudo-tumor.

Since then, I have had about 10 other cases, in most of which visualization was not successful, except in 1 case, in which there was a tumor of the thyroid with several metastases.

The method of injection of air is important. I believe it is necessary to inject the air into the lower portion, but it should also be injected into the upper portion of the orbit. In the latter area, injection of air is made just beneath the periosteum, with the introduction of the needle far back into the orbit. Air must be injected slowly. I have found that with rapid introduction of air there was a more rapid escape into the lids, with resulting haziness in the roentgenogram.

DR WENDELL L. HUGHES, Hempstead, N. Y. Dr. MacLean spoke of the use of air in trephining. In a conversation I had with Dr. J. A. MacMillan a few days ago, he said that he had had difficulty in keeping the air in the anterior chamber. A simple way of accomplishing this is by placing the head far back over a shoulder pillow, the posture will make the difference between having the air pass under the flap or enter the anterior chamber. If the head is held far back, practically all the air will be retained in the anterior chamber. This is readily controlled by posture, which is important in the use of air.

Three cases reported by Dr. C. S. O'Brien,¹² who had been using air routinely after cataract extraction, were interesting. He said that

¹² Reported in a paper read at the Eighty-First Annual Meeting of the American Ophthalmological Society, Nov. 12, 1945.

he allows his patients to sit up directly after the operation and does not place them flat in bed, as some of us who are more conservative do. He said that in these 3 cases glaucoma developed because the air had apparently got behind the iris. It is readily seen how, if the patient stooped forward to tie his shoe or pick up something from the floor, the iris would fall forward and the air would slip behind the iris and stay there. Dr O'Brien said that in 2 of the cases the glaucoma was stubborn, but that in the third case the condition was readily cured by shaking the patient when upside down and getting the air out from behind the iris. He said that with this maneuver the glaucoma was immediately relieved. I wish one could cure all glaucomas that way.

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ANGIOID STREAKS OF THE FUNDUS OCULI OBSERVED OVER A PERIOD OF THIRTY-SIX YEARS

Report of a Case

WILLIAM ZENTMAYER, M D
PHILADELPHIA

A BRIEF abstract of the clinical history of a typical case of angioid streaks of the fundus oculi observed over a period of thirty-six years is here given. The case was presented before the American Ophthalmological Society in 1909¹ and was repeatedly reported on over a period of several years before the section on ophthalmology of the College of Physicians of Philadelphia.

REPORT OF CASE

A man aged 33 came to the eye clinic at St. Mary's Hospital in November 1908, complaining of pain and dimness of vision in the right eye. This was due to a dendriform ulcer of the cornea. In the routine examination the angioid streaks in the retina were revealed. The clinical picture at that time was as follows. In the fundus of each eye there was a system of ramifying and interlacing pigmented streaks extending outward into the fundus from a similar band which surrounded crescents of grayish yellow retinochoroidal disturbance about the disk. The streaks were beneath the retinal vessels, had serrated borders and extended toward the periphery of the fundus, which was the site of conspicuous retinochoroidal changes. The streaks were in general black, but in places there were islands of bright red. In the left eye there was a horizontal oval hemorrhage below the fovea.

In 1934, at the request of Dr. T. L. Terry,² I had studies again made of the patient's physical condition to determine whether there was any evidence of osteitis deformans. The roentgenograms were negative for evidence of this disease, but there was some calcification in the region of the sella turcica, probably within the internal carotid artery. At this time there was no longer any evidence of the former angioid streaks, and in the right eye there was an area beneath the superior temporal vessel suggestive of circinate retinitis.

The patient was seen again on May 18, 1944. In the right eye there were a few vacuoles in the lens. The disk was somewhat waxy in appearance, but the gray zone which was formerly present about the disk had disappeared. Over most of the fundus there was pronounced sclerosis of the choroidal vessels, with deep pigmentation of the intervacular spaces. In the macular region there were

An abstract of this paper was published in the July 1945 issue of the *ARCHIVES*, p. 70.

Read before the Section on Ophthalmology of the College of Physicians, of Philadelphia, April 19, 1945.

1 Zentmayer, W. *Tr. Am. Ophth. Soc.* **12**: 267, 1909.

2 Terry, T. L. *Tr. Am. Ophth. Soc.* **32**: 555, 1934.

masses of dense pigment, of irregular shape. In some portions of the fundus there was complete atrophy of the choroid. In the left eye the general appearance of the fundus was about the same as in the right eye, but the areas of complete destruction of the choroid were more extensive, and there was denser massing of the pigment in the macular region. There were two large areas of almost complete atrophy, one along the course of the inferior nasal vessel and the other along the course of the inferior temporal vessel. Beneath the superior temporal artery there was a vertical irregular area 3 disk diameters in size, of whitish hue with a circinate appearance. Vision was 1/60 in each eye.

COMMENT

Bedell³ stated that the narrow circumpapillary atrophy as such has nothing to do with the streaks and, furthermore, that when degenerative macular lesions develop they follow the usual clinical course of deep retinal or superficial choroidal hemorrhages, exudate, edema, an expanding ring of blood and increasing exudate. After many months the recurring hemorrhages stop, the exudate becomes organized, and the scar persists throughout life. Bedell did not conceive of this process as an integral part of angioid streaks. He further stated that he did not believe that the ruptures in Bruch's membrane and the accompanying pseudoxanthoma elasticum are part of the same process, certainly not in all patients.

There seems still to be among clinicians want of a proper conception as to what constitutes angioid streaks, and there exists among pathologists a diversity of opinion as to the genesis of such streaks and the significance of associated systemic conditions. Angioid streaks constitute a clinical entity. The diagnosis is based on the presence of a more or less broken peripapillary ring of pigment from which pigmented streaks extend out into the fundus. The appearance of the streaks varies from dark red to brown, or even black. The edges of the streaks are serrated, and along their course there may be reddish dots. They lie beneath the retinal vessels. Usually there is a complete or incomplete narrow grayish zone about the papilla. The entire fundus may have a mottled appearance, or these degenerative changes may appear only in the periphery. Both eyes are involved.

One or more pigment streaks in the fundus no more constitute angioid streaks than does one or more stars in the heavens make a constellation. Siegrist⁴ has called attention to the formation of pigmented dots along the course of sclerosed choroidal vessels. Verhoeff⁵ stated that pigment streaks sometimes result from separation of the choroid

3 Bedell, A. J. *Am J Ophth* 28 601 (June) 1945.

4 Siegrist, A. *Internat Ophth Cong*, Utrecht, 1899, p. 131.

5 Verhoeff, F. H. *Nature and Origin of Pigmented Streaks Caused by Separation of the Choroid*, *J A M A* 97 1873 (Dec 19) 1931.

These, and still other causes, exist, and the condition may be simulated by the line of demarcation in spontaneous replaced retina or by remnants of old hemorrhages, but, as Verhoeff pointed out, these do not produce the characteristic picture of the condition known as angioid streaks

Cases of angioid streaks have been supposed to be uncommon, but in discussion Clay stated that since his first report, in 1932,⁶ he has seen 63 more cases. The clinical notes on these cases have not yet been published

The end results, as demonstrated in my own case, I conceive to be an integral part of angioid streaks, and not a superimposed, nonrelated condition, and it is probable that in most cases in the course of years there will appear extensive changes in the choroidal vessels, with macular hemorrhages and accumulations of pigment in the central area, for this reason the prognosis from the beginning should be guarded, notwithstanding that vision and fields may be normal

With the histologic changes pointing strongly to a pathologic process in Bruch's membrane as the cause of angioid streaks, it seems logical to assume that when this condition and pseudoxanthoma elasticum exist in the same patient, as they did in 57 of 67 cases collected by Goedbloed⁷ in 1938, they are part of a common process, probably a generalized degeneration of elastic tissue. The association of pseudoxanthoma elasticum and angioid streaks occurs far more frequently than present statistics show. The fact that one may exist without the other at the time the condition is first seen in a patient does not invalidate this assumption, as in the presence of either lesion the other may develop later, as both pursue a long course. That other general conditions, such as osteitis deformans, may be associated with angioid streaks is well known. Gronblad⁸ stated that mesenchymatous atrophies and dystrophies can determine characteristic and similar changes in the fundus

Numerous theories had been advanced previous to the recognition by Gronblad and Strandberg⁹ that angioid streaks and pseudoxanthoma elasticum are frequently associated and previous to any report on the histologic character of the streaks. The earliest view was that they were hemorrhagic in origin and that the blood in some manner, possibly anatomically, metamorphosed into streaks. This was Doyne's¹⁰ expla-

6 Clay, G. Angioid Streaks of the Retina and Pseudoxanthoma Elasticum, *Arch Ophth* 8:334 (Sept) 1932

7 Goedbloed, J. Syndrome of Gronblad and Strandberg, *Arch Ophth* 19 1 (Jan) 1938

8 Gronblad, E. *Acta ophth (supp 1)* 10 1, 1932

9 Gronblad, E. *Acta ophth* 7 329, 1929

10 Doyne R W. *Tr Ophth Soc U Kingdom* 9.128, 1889

nation and was accepted by most of the earlier authors—de Schweinitz,¹¹ Holden¹² and Pagenstecher¹³. Later, as a result of the discovery by Lister¹⁴ of new vessels in eyes that had been the seat of endophthalmitis, Doyne made the suggestion that the angioid streaks might be new vessels. This view was accepted by a number of authors, including Holloway¹⁵ and myself¹⁶.

A variant of the hemorrhagic theory was that advanced by Collins,¹⁷ namely, that they represent the posterior ciliary vessels, in the perivascular sheaths of which hematogenous pigment from choroidal hemorrhages had been deposited.

Later theories center about the changes noted in Bruch's membrane Verhoeff,¹⁸ as a result of his studies of an eye the fundus of which had never been studied ophthalmoscopically and which had many other pathologic features, reported that angioid streaks were due to ridges in Bruch's membrane resulting from the contraction of a layer of fibrous tissue, which had replaced the deeper layers of the choroid. Verhoeff¹⁹ stated in 1944 that the observations of Bock had almost, but not quite, persuaded him that his own case had not been one of angioid streaks.

Both Bock²⁰ and Hagedoorn²¹ observed degeneration of Bruch's membrane with numerous ruptures which corresponded to the distribution of the angioid streaks. Hagedoorn found that the choroid was sclerosed and thickened. The degeneration of the elastic fibers impairs the translucence of the membrane, and this is the cause of the gray or dotted appearance of the fundus.

Law²² found plications of the retina, with the intervening space filled with pigment debris.

Clinical support of involvement of Bruch's membrane is found in the report by Gifford and Cushman²³ of a case of angioid streaks associated

11 de Schweinitz, G. E. *Ophth. Rec.* **6** 325, 1897, *Tr. Am. Ophth. Soc.* **8** (pt. 3) 650, 1896.

12 Holden, W. *Arch. Ophth.* **24** 147, 1895.

13 Pagenstecher, H. E. *Arch. f. Ophth.* **67** 298, 1908.

14 Lister, W. T. *Ophth. Rev.* **22** 151, 1903.

15 Holloway, T. B. *Tr. Am. Ophth. Soc.* **25** 173, 1927.

16 Zentmayer, W. *Tr. Coll. Physicians, Philadelphia* **49** 216, 1927.

17 Collins, E. T. *Tr. Ophth. Soc. U. Kingdom* **43** 273, 1923.

18 Verhoeff, F. H. *The Nature and Pathogenesis of Angioid Streaks in the Ocular Fundus*, *Tr. Sect. Ophth., A. M. A.*, 1928, p. 243.

19 Verhoeff, F. H., in discussion on Bedell,³ p. 615.

20 Bock, J. *Ztschr. f. Augenh.* **95** 1, 1938.

21 Hagedoorn, A. *Angioid Streaks*, *Arch. Ophth.* **21** 746 (May), 935 (June) 1939.

22 Law, F. W. *Tr. Ophth. Soc. U. Kingdom* **58** 191, 1938.

23 Gifford, S. R., and Cushman, B. *Certain Retinopathies Due to Changes in the Lamina Vitrea*, *Arch. Ophth.* **23** 60 (Jan.) 1940.

with hyalin deposits in the lamina vitrea and in the case of a girl of 14 whom I saw in consultation with Dr Warren S Reese and who showed fundic changes strongly resembling Doyne's honeycomb degeneration. Two years later angioid streaks were observed to be forming.

From present evidence it is probable the condition known as angioid streaks is due to degeneration of Bruch's membrane, in which tears or ruptures occur, that the hemorrhages seen at various stages of the condition result from similar lesions in the walls of the blood vessels and that the later destructive changes in the macula are part of the syndrome. The gray, or partial, zone about the papilla may be due to the changes in Bruch's membrane, as it is the only layer of either the retina or the choroid which reaches the optic nerve, and it is much thicker in this area than elsewhere.

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BITEMPORAL DEFECTS IN THE VISUAL FIELDS RESULTING FROM DEVELOPMENTAL ANOMALIES OF THE OPTIC DISKS

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ONE of the most dependable axioms in ophthalmology is that bitemporal hemianopsia indicates a lesion at the optic chiasm. The following cases demonstrate that even to this rule there may be exceptions which can occasionally cause difficulty in diagnosis.

REPORT OF CASES

CASE 1—A man aged 31 complained of thoracic pain on exertion, which was considered by his internist to be due to angina pectoris. In the course of his examinations the patient requested refraction, although he had not had any ocular symptoms. Refraction indicated that the following correction was required: right eye, -0.25 D sph $\cap -1.75$ D cyl, axis 140, left eye, -0.75 D sph $\cap -1.50$ D cyl, axis 170. The visual acuity of 6/12 in each eye afforded by these lenses did not satisfy the refractionist, consequently, he requested further studies.

Ophthalmoscopic examination (fig 1A) disclosed a downward tilting of the optic disks and small inferior crescents. The limits of the visual field, as defined on the perimeter, were normal, but on the tangent screen at 1 meter the isopters for the 1 and the 2 mm white beads were contracted temporally and superiorly (fig 1B). As I suspected a chiasmal lesion, I requested that the patient have a complete neurologic examination, determination of the basal metabolic rate and roentgenographic examination of the head and sella turcica. None of these examinations disclosed any abnormality.

The patient was advised to return for further observation in six months. When he returned, eleven months later, he complained of abdominal discomfort when his stomach was empty. Roentgenologic study of the gastrointestinal tract demonstrated no evidence of disease. Visual acuity and the visual fields showed no change since the first examination. The absence of progression of the defects of the visual fields proved that no chiasmal lesion was present.

This case is an example of congenital distortion of the optic disks causing depressed areas in the visual fields in the region of the normal blindspots. On the tangent screen these fields gave the impression of bitemporal hemianopsia. These defects of the visual fields differ, however, from those encountered with ordinary chiasmal lesions, such as those produced by hypophysial tumors. In the latter condition there is usually a splitting at the midline, the defect of the field is limited to the area on the temporal side of the midline, and the area on the nasal side is spared.

From the Section on Ophthalmology, the Mayo Clinic

In case 1, in which bitemporal hemianopsia resulted from anomalous optic disks, the isopters passed from the temporal into the nasal fields with no deflection at the midline

CASE 2—A woman aged 45 complained of pain which had been present over the left side of her body for five years. Her husband said she had always been sick. Complete general physical examination did not disclose any evidence of an organic lesion. The diagnosis was cardiac neurosis and chronic indigestion.

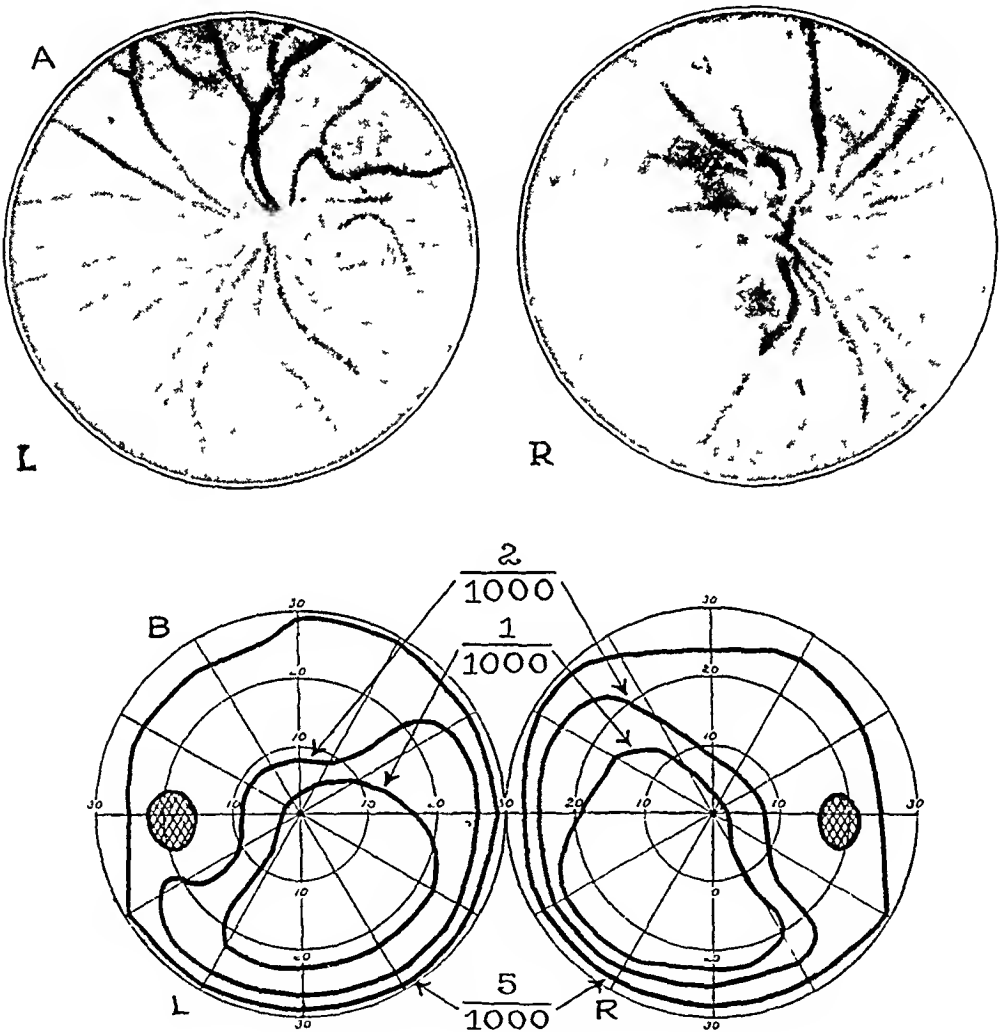


Fig 1 (case 1)—A, tilted optic disks, B, bitemporal hemianopsia

The patient had no ocular symptoms. She was wearing the following correction for a high degree of myopia: right eye, -10.25 D sph -1.75 D cyl, axis 127, vision 6/20; left eye, -10.75 D sph -2.00 D cyl, axis 63, vision 6/20.

Ophthalmoscopic examination disclosed large inferior choroidal crescents (fig 2A). The optic disks appeared to be tilted downward. Although the peripheral limits of the visual fields were normal, there was a bitemporal depression demonstrable with small targets on the tangent screen (fig 2B). This was believed to be due to the congenital anomaly of the optic disks.

CASE 3—A woman aged 34 had had frontal headaches for fifteen years before she came to the clinic. The headache had become worse during the past three

hemianopsia. Roentgenograms of his sella turcica had been made at once but had not disclosed any abnormality. As he was worried, he sought another opinion.

Perimetric fields (fig. 4) were plotted with several sizes of test objects. The periphery on the perimeter was normal. On the tangent screen at 1 meter the field for the 1 mm white bead was contracted temporally in both eyes. There was undoubtedly a bitemporal hemianopsia. However, in the field for the right eye the isopter for this test object sloped upward from the temporal into the nasal field without in any way stepping up as it crossed the midline. I assured the patient that in my opinion his bitemporal hemianopsia did not indicate a chiasmal lesion, but that it was merely the result of a disturbance in the retina and possibly was associated with a refractive error.

He was wearing the following correction, which gave him 6/5 vision in each eye — 50 D sph \ominus +200 D cyl, axis 118 on the right and +0.25 D sph \ominus +0.50 D cyl, axis 65 on the left. Ophthalmoscopic examination disclosed optic disks of normal color with distinct margins and small central physiologic cups. Below each disk the choroid was thin, a probable explanation for the defects of the visual fields.

The patient has returned for observation over a period of six years, and there has been no further change in his visual fields. He is well and shows no evidence of pituitary tumor.

CASE 5—A woman aged 39 complained of poor vision and of headache and came to the clinic for examination because she feared she had a brain tumor. She said that all her life her vision had been poor but that she had worn glasses only occasionally because they spoiled her appearance. She had had attacks of headache since childhood usually at the time of her menses.

A month before she came to the clinic, she had consulted an oculist because of these difficulties. He had told her that her vision was failing. His office girl had plotted the patient's visual fields and had found a defect which made the oculist suspect that she had some disease of the brain. He had referred her to an otolaryngologist, who had found some peculiar responses to vestibular tests which he had interpreted as indicative of a tumor of the brain. She had then been referred to a neurologist.

When the patient had learned that it was suspected that she had a tumor of the brain, she had become alarmed and had consulted several more physicians. Finally, she had had a nervous breakdown. For two weeks before she came to the clinic she had had pain on the right side of her face and had thought that the right side of her body was becoming paralyzed.

Examination of her eyes disclosed that with her correction the visual acuity in each eye was 6/15 on the Snellen chart and 14/14 on the American Medical Association reading card. She was wearing the following lenses: right eye, —4.50 D sph \ominus —2.50 D cyl, axis 168; left eye —3.75 D sph \ominus —3.75 D cyl, axis 15. Ophthalmoscopic examination disclosed that the optic disks were tilted obliquely downward (fig. 5A). This caused a difference of 2 D between the level of the retina on the superior temporal side and that on the inferior nasal side of the disks, the latter portion was the farther back. Except toward the lower part of the periphery, there was relatively little choroidal degeneration. Plotting of the visual fields disclosed bitemporal hemianopsia (fig. 5B). This was not demonstrated on the perimeter but was shown only on the tangent screen with small test objects. The isopter for the 1/1,000 target passed smoothly from the temporal into the nasal half of the visual field without any deflection at the midline. This suggested that the defects were not due to a chiasmal lesion but, rather, resulted

from changes in the eyeballs. The ophthalmologist expressed the opinion that his examinations revealed no evidence of a tumor of the brain.

General physical, neurologic and roentgenographic examinations failed to disclose any evidence of disease. The neurologist's diagnosis was mild depression and anxiety state. The patient was assured that there was no evidence of a tumor of the brain.

CASE 6—A Mexican woman aged 30 came to the clinic because she had been told she had a tumor of the brain. At the age of 4 years she had had bilateral otitis media, this had been followed by chronic suppurative otitis media,

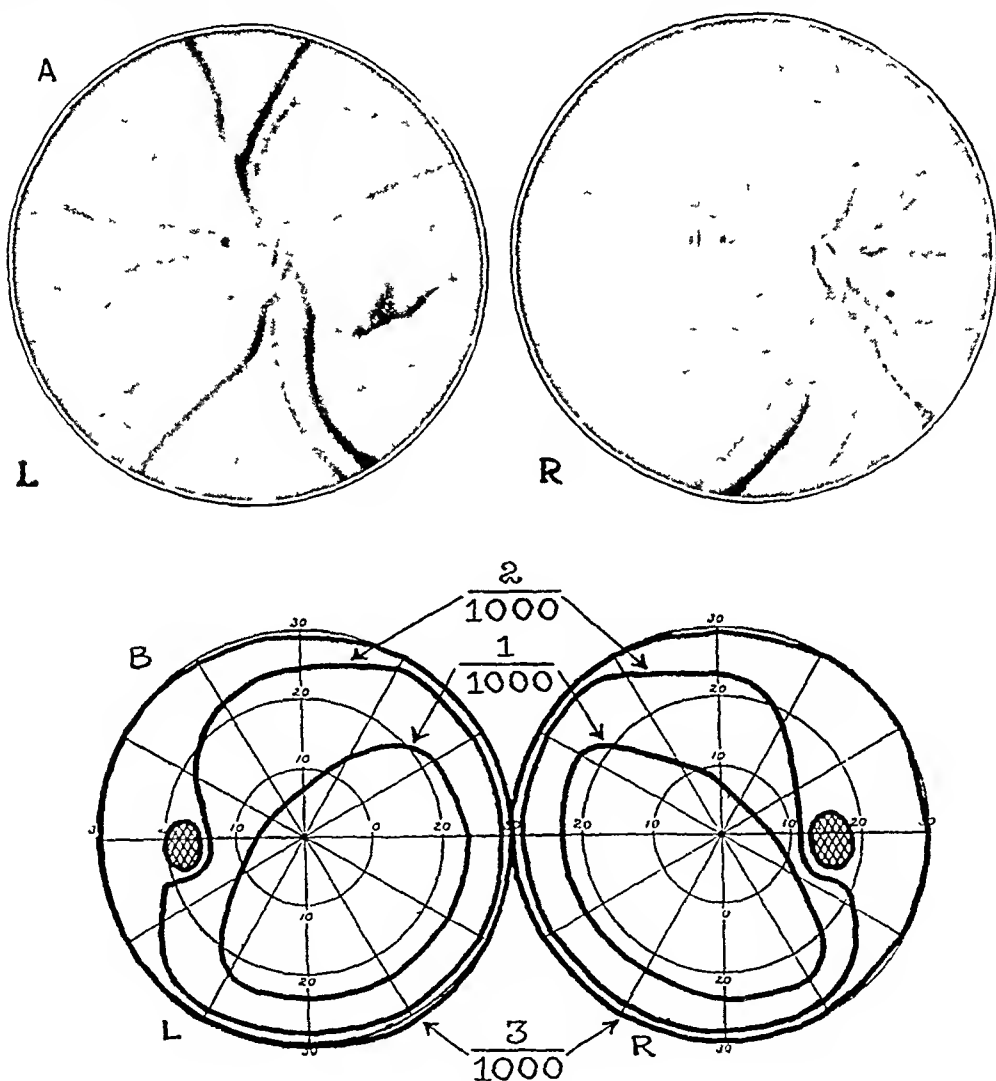


Fig 5 (case 5) —A, tilted optic disks, B, bitemporal hemianopsia

which had lasted for many years. For six years she had had occasional attacks of headache associated with nausea and vomiting. Four months before she came to the clinic she had had a sudden attack of pain in the left temporal region and paralysis of the left side of the face, accompanied with vertigo and nystagmus. Radical mastoidectomy, which had been performed a few days later, apparently had relieved the paralysis, although the other symptoms had persisted and the left ear had become completely deaf. Two weeks later consultation had disclosed ataxia, mild adiadokokinesis, dysmetria of an upper extremity and hypesthesia of the left cornea and pharynx. A pneumoencephalographic examination had been

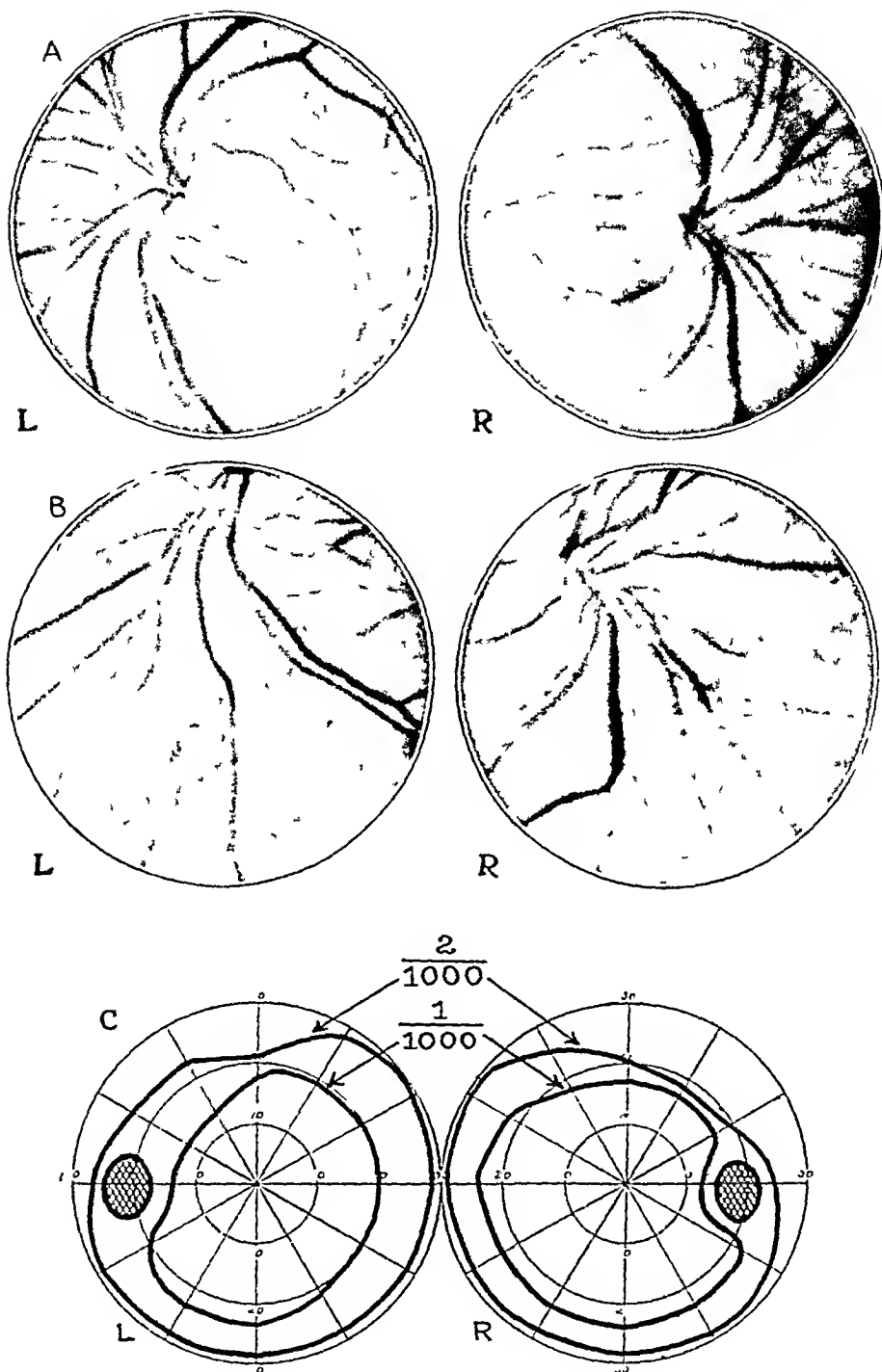


Fig 6 (case 6) — *A*, small, crowded optic disks, *B*, thin choroid inferiorly, *C*, bitemporal depression of the visual fields

performed, but the results had been inconclusive because no air had entered the ventricles. Subsequently, the sensation on the left side of her face had become impaired. Her physician had suspected that she had a tumor of the cerebellopontile angle.

About this time her physician in México, D F, had suggested that she seek further medical aid. After she had left Mexico, she had improved rapidly. Her gait had become normal, and the paralysis and loss of sensation of the left side of her face had disappeared almost completely.

General physical and neurologic examination at the clinic did not disclose any abnormality except a dead labyrinth on the left side, which the otolaryngologist considered to be the result of a previous attack of acute labyrinthitis. Examination of the eyes showed that visual acuity was 6/15 in the right eye and 6/12 in the left eye with her correction of -3.00 D cyl, axis 145 for the right eye and -0.75 D sph $\cup -1.00$ D cyl, axis 32 for the left eye. Ophthalmoscopic examination disclosed structurally full optic disks. The margins of the disks were blurred, as all the vessels were crowded into the nasal half of each disk (fig 6A). The choroid was thin (fig 6B) except at the central area, partly as a consequence of myopia and partly because the patient was very blonde.

Plotting of the visual fields disclosed bitemporal hemianopsia (fig 6C). This was evident only on the tangent screen, not on the perimeter. Because of the accompanying myopic astigmatism and the thinning of the choroid, this condition was considered to be the result of local changes in the eyes, and not to be indicative of a chiasmal lesion.

COMMENT

The types of field defects illustrated in these cases have been recognized for many years and are briefly described in two of the current standard textbooks on perimetry. Peter¹ mentioned the not infrequent occurrence of scotomas and other defects of the visual field in the presence of congenital anomalies of the optic disk. Traquair² mentioned the presence of juxtacecal scotomas in cases of myopia. In recent years there has been little consideration of the defects of the visual fields produced by congenital anomalies of the optic disk in either British or American journals. An exhaustive article by Ziering³ appeared in Germany in 1936, and one by Baba⁴ appeared in Japan in 1939.

Clinicians have apparently regarded these defects as nuisances which add to the already difficult task of charting the visual fields accurately and have not regarded them as sufficiently important in themselves to justify exhaustive study. I am inclined to agree with this attitude, and I have not attempted to plot the visual fields in a large number of cases in which the optic disks were anomalous.

When one suspects that a bitemporal hemianoptic depression is due to anomalous disks rather than to a chiasmal lesion, one may sometimes obtain help by observing the way the defect behaves at the midline. If

1 Peter, L. C. *Principles and Practice of Perimetry*, ed 4, Philadelphia, Lea & Febiger, 1938, pp 169-170.

2 Traquair, H. M. *An Introduction to Clinical Perimetry*, ed 3, St. Louis, C. V. Mosby Company, 1938, p 95.

3 Ziering, J. *Der papillare und parapapillare Conus heterotypicus*, *Klin Monatsbl f Augenh* **97** 169-184, 1936.

4 Baba, M. *Ueber den Conus nach unten und das Gesichtsfeld*, *Nagasaki Igakkwai Zasshi* **17** 2497, 1939.

it passes smoothly from the temporal into the nasal field without deflection, it is likely the result of distortion of structures at the nerve heads. A distinct step at the midline occurs in association with chiasmal lesions.

SUMMARY

Congenital anomalies of the optic disks may cause depressed areas in the visual fields in the region above the normal blindspots. Since these are located temporal to the fixation points, they give on the tangent screen the appearance of relative bitemporal hemianopsia. They do not often disturb the isopter for the 3 mm bead on the perimeter.

STUDIES ON DARK ADAPTATION IN MILITARY PERSONNEL COMPLAINING OF "NIGHT BLINDNESS"

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A FAIRLY common complaint of patients seen by the ophthalmologic service in the theater of operation is poor night vision. It constitutes a considerable problem both from a diagnostic and from a therapeutic standpoint. During the summer of 1944 my associates and I carried out a study of a group of United States soldiers under the direction of Major Trygve Gunderson, ophthalmologic consultant for the armed forces of the United States in the Mediterranean Theater. At this time we were fortunate to have placed at our disposal the equipment of the department of ophthalmology of the University of Rome, and generous help was given by staff members, especially Prof. Giambattista Bietti, on leave from the University of Sassari, Sardinia.

The following paper is a report of the observations on this group.

METHOD

All patients were given a careful ophthalmologic examination, including determination of visual acuity, cycloplegic refraction, funduscopy, examination with the slit lamp, and study of central and peripheral fields, before the initial determination of dark adaptation was made. After the first determination, patients with low readings were submitted to a neuropsychiatric examination.

Tests for dark adaptation were made after preliminary bleaching of the visual purple, accomplished by having the patient gaze at a well illuminated white sheet for ten minutes. The patient was then placed in a dark room and seated 1 meter in front of a Nagel adaptometer. Readings were taken of the patient's dark adaptation at one, fifteen, thirty and forty-five minutes. No correction was made for pupillary size.¹ The patient was instructed to keep his eyes closed between readings. Results were plotted on a semilogarithmic scale in Nagel units, this unit being the reciprocal of the 1 meter Hoeffner candle.

CLINICAL MATERIAL

Sixty-six patients were examined. As controls, 14 patients were examined who gave positive statements that they had no visual difficulty at night. As far as possible, these controls were soldiers who did "black-out" driving and infantrymen who had been on frequent night patrol.

Thirty-nine of the patients complained of "night blindness" and were seen by staff members of the department of ophthalmology as hospital patients, with a diagnosis of "amblyopia nocturnal."

¹ Sloan, L. L. Instruments and Techniques for Clinical Testing of Light Sense, *Arch Ophthalmol* 24:258 (Aug) 1940.

Thirteen patients were admitted to the hospital with a diagnosis of infectious hepatitis. Interest was stimulated in the relationship of hepatic disease and night blindness by the admission of an officer complaining of "night blindness" which developed approximately six weeks after the onset of hepatitis.

NORMAL CONTROLS

The 14 men with no history of visual difficulties at night gave normal final readings, and readings taken at one, fifteen, thirty and forty-five minutes on the adaptometer, when plotted on a semilogarithmic scale, produced a simple curve with the convexity upward.

No patient in this group showed a refractive error of more than 1.00 D under homatropine cycloplegia. Visual acuity with correction was 20/20 or better in all cases. Examination with the slit lamp revealed

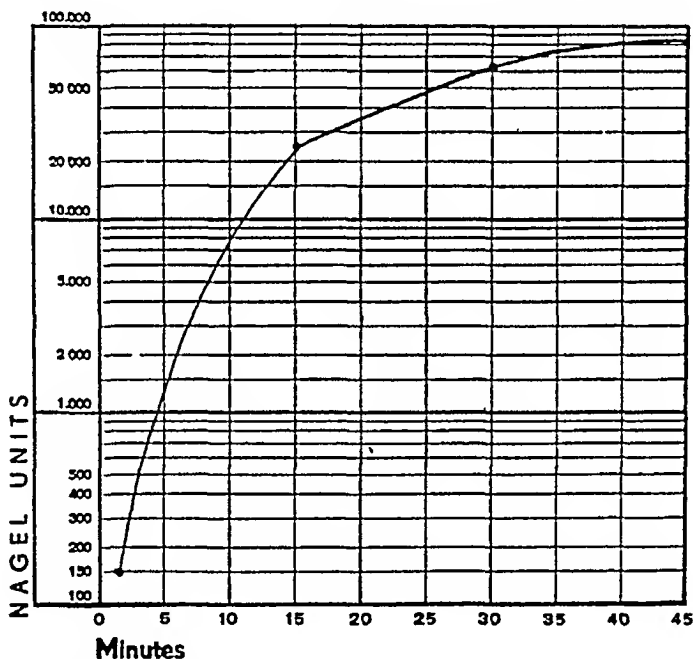


Fig 1—Curve for dark adaptation readings. Visual acuity was 26/16 in each eye with a correction of +0.25 D sph \ominus +0.75 D cyl, axis 90 for the right eye and +0.75 D cyl, axis 80 for the left eye (cycloplegic refraction).

nothing pathologic nor did studies of the fundus and visual field show any abnormalities.

The final normal readings on the Nagel adaptometer range from 50,000 to 150,000 Nagel units after forty-five minutes of dark adaptation. In general, all readings taken at one minute can be disregarded. In our series, this was true for two reasons:

1. After the bleaching, regeneration of visual purple in the rods is negligible for the first few minutes. Dark adaptation during this period is primarily due to the regeneration of iodopsin, a substance in the cones.

2 Patients were tested in groups of 3, and by the time the initial reading had been taken on the third patient a period of two or three minutes had elapsed

Secondary adaptation is accomplished by a substance in the pigment of the rods. This photosensitive pigment is known as rhodopsin and is formed in the pigmented epithelium of the retina by a combination of a protein and vitamin A. The regeneration of this substance is fairly rapid for the first thirty minutes but is not complete until after forty-five to sixty minutes, when for all practical purposes a maximum of light sensitivity has been reached. When plotted on a semilogarithmic scale, readings of the dark adaptation taken at one, fifteen, thirty and forty-five minutes will describe a simple curve with convexity upward. It is obvious that, no matter what the degree of night blindness, when the readings taken at one, fifteen, thirty and forty-five minutes are plotted on a semilogarithmic scale a curve of this family will result, since it represents the physiologic regeneration of visual purple, which is progressive until a maximum is reached.

PATIENTS COMPLAINING OF NIGHT BLINDNESS

The 39 patients with the diagnosis of night blindness can be divided into two groups. The first group consists of 5 patients who thought that their visual difficulty at night was of moderate degree and not incapacitating, and the second, of 34 patients, who believed it to be of sufficient severity to make them of little or no use on front line duty.

The 5 patients complaining of a moderate degree of night blindness gave normal adaptation curves. Three of the 5 patients had a refractive error of 1.50 D or more. Corrected visual acuity in this group was 20/30 or better in all cases. Examination with the slit lamp revealed no pathologic process, and studies of the fundus and visual fields showed no abnormalities. This group of 5 patients was returned to full duty. The examination and the reassurance gained from the examination apparently were sufficient to convince them that their doubts concerning good vision at night were without basis.

The 34 patients who complained of severe night blindness were less easy to dispose of. Initial readings on this group revealed 6 men with normal dark adaptation curves. Three of the group of 6 patients had a refractive error of 1.50 D or more. Corrected visual acuity was 20/30 or better in all cases. Examination with the slit lamp, funduscopy study and examination of the visual fields did not show any pathologic condition.

Detailed histories in all 6 cases revealed that some experience had occurred which had convinced the patient that his night vision was inadequate. These experiences were in effect emotional traumas, and in some cases had been repeated. While some of these traumas were

slight, others were of considerable severity. In each instance the patient felt that because of his poor night vision he had failed in a specific job. A soldier on night patrol in which a number of men are lost reviews the experience and attaches great importance to remarks made by other members and to their reactions. This is magnified if he is in charge of the patrol, since he feels a sense of responsibility for loss of the members. In explaining his reactions to the situation, he will often attempt to find some physical disability which is responsible for something he has or has not done. Since vision is of utmost importance, it is one of the first physical capabilities to come under scrutiny. It is not uncommon for soldiers on front line duty to compare their vision at night, and, while a given soldier's night vision may be adequate, his

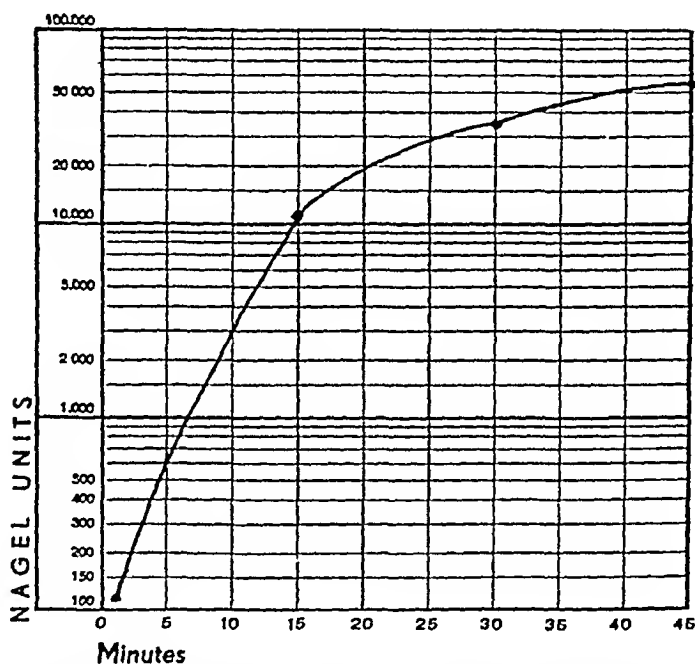


Fig 2—Curve for dark adaptation readings. Visual acuity was 20/100 in each eye without correction. With a correction (cycloplegic refraction) of -3.00 D sph $\cup +2.25$ D cyl, axis 5 for the right eye and of -3.00 D sph $\cup +1.25$ D cyl, axis 160 for the left eye, vision was 20/20 in each eye.

The patient was reduced from the rank of sergeant to private and was relieved as a tank driver for "sideswiping" an oncoming truck at night. The officer who reduced him asked that he be hospitalized for "night blindness."

finding of some one with better night vision tends to increase the belief that his is below standard. Not all soldiers have been taught how to use their visual apparatus at night. Too often they attempt to fix objects on the fovea, where vision is poorest.

The group of 6 patients with initial normal dark adaptation curves all returned to full duty once it was explained to them that their dark adaptation had been found to be normal. They were given a few instruc-

tions concerning seeing at night, such as use of a searching movement to discern objects in the dark and not to look directly at, but slightly to one side of, the object for best detail

The remaining 28 patients all had initial low final dark adaptation readings. Five of these patients had subnormal final readings for which no cause could be found. The dark adaptation curves followed the normal configuration, being simple curves with the convexity upward.

Only 2 of the 5 patients showed a refractive error of more than 1.00 D. These 2 patients were myopic. Corrected central vision in all 5 cases was 20/20 or better. Examination with the slit lamp revealed nothing pathologic, nor did studies of the fundus and visual fields show any abnormalities. No family history of night blindness could be elicited.

Neuropsychiatric consultation of this group of 5 patients revealed stable personalities. Two of these patients were given a preparation containing 40,000 U. S. P. units of vitamin A daily, without improvement. These patients were considered to have simple night blindness, which may be a hereditary condition.

Duke-Elder² stated that in hereditary transmission night blindness exhibits three tendencies: (a) a dominant form, (b) a recessive form, frequently associated with myopia, and (c) a recessive, sex-linked form, usually associated with high grade myopia, and transmitted through unaffected daughters of affected males to some of their sons.

It was impossible to prove that any of the patients studied had any particular form of night blindness, since we were dependent on the patient's history rather than on a study of members of his family.

Four of the group of 28 patients with initial low final readings had dark adaptation curves which followed the normal configuration, but examination revealed ocular defects. In all 4 patients funduscopy showed retinitis with pigmentary degeneration. Two had associated changes in the lens. The visual fields of all 4 patients showed extreme constriction of the peripheral fields for form.

Since visual purple is a component of the rod cells, which are more concentrated in the periphery of the retina, diseases of this region and disturbances of the pigment where resynthesis appears to take place would cause a decrease in the light sensitivity. The regeneration, however, would not be altered in unaffected areas, hence, the dark adaptation curve would follow the normal configuration when plotted.

For the remaining 19 patients the readings were extremely low and could not be explained by funduscopy changes, heredity or dietary deficiency. On initial examination 5 patients showed not only low final readings but abnormal configuration curves for dark adaptation.

² Duke-Elder, W. S. *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1938, vol. 1, p. 982.

Of the 19 patients, 11 had corrected visual acuity of less than 20/40. Twelve patients had refractive errors of more than $+$ or -1.50 D. Fundusoscopic study revealed no gross pathologic changes. The visual fields showed a great variety of patterns. Some were normal, others showed from 10 to 30 degrees of constriction at the periphery. Very irregular fields were infrequent.

It was difficult to explain the results of examination in this group of patients. Some patients had histories that suggested psychoneurosis, but it was evident that it would be difficult to prove that night blindness was a hysterical manifestation. Also, abnormal configuration curves of dark adaptation were present and had to be explained.

The first step was to recheck the dark adaptation in this group. This gave valuable information. For the most part, patients showing a normal configuration curve initially on second examination showed a curve of the same family, although the final reading was often such as to preclude the probability of range of error. Patients with abnormal initial configuration curves were not consistent on second examination, so far as configuration curves or final readings were concerned. It was thought that these observations could be explained by dividing this group into two subgroups. Since the men having an abnormal configuration of the dark adaptation curve gave such inconsistent answers, it was conceivable that they were wilfully misinterpreting their readings. The results for the group with normal configuration curves and low final readings could be accounted for by a suppression of dark adaptation.

Wilful misinterpretation or malingerings, which in the dark adaptation test could be accomplished by giving inaccurate answers, might explain the results for the first group. It would be difficult for a subject to give similar readings one week apart and a matter of chance that a normal configuration curve of dark adaptation could be produced by plotting the results. Hysteria would explain the results for the patients with normal configuration curves of dark adaptation. Since the mechanism of hysteria is at an unconscious level, the suppression of dark adaptation would occur equally in all readings, and a normal configuration curve would result. It was found that many of the group giving normal configuration curves but low final readings showed manifestations of psychoneurosis such as hysterical amblyopia and regular constriction of the peripheral form fields.

By dividing the 19 patients into two such groups, it was possible to apply a test to confirm the belief that the one group was consciously misinterpreting the readings. The optokinetic drum was utilized for this purpose. It has been known to the Italian medical corps for some time and has been used to detect persons feigning blindness. The principle of the test is as follows. When a series of moving objects traverses the field of vision, the eyes follow one object until its successor obtrudes

itself into consciousness. When this happens, the fixation reflex comes into play, and the second object is fixated. This produces a nystagmus commonly known as "optokinetic," or "train," nystagmus. Since the nystagmus is involuntary, the test is absolute as soon as the patient can discern the moving objects.

Professor Bietti constructed an electrically driven optokinetic drum measuring about 24 inches (60 cm) in diameter and about 18 inches (45 cm) in height. Alternate stripes of black and white paper were

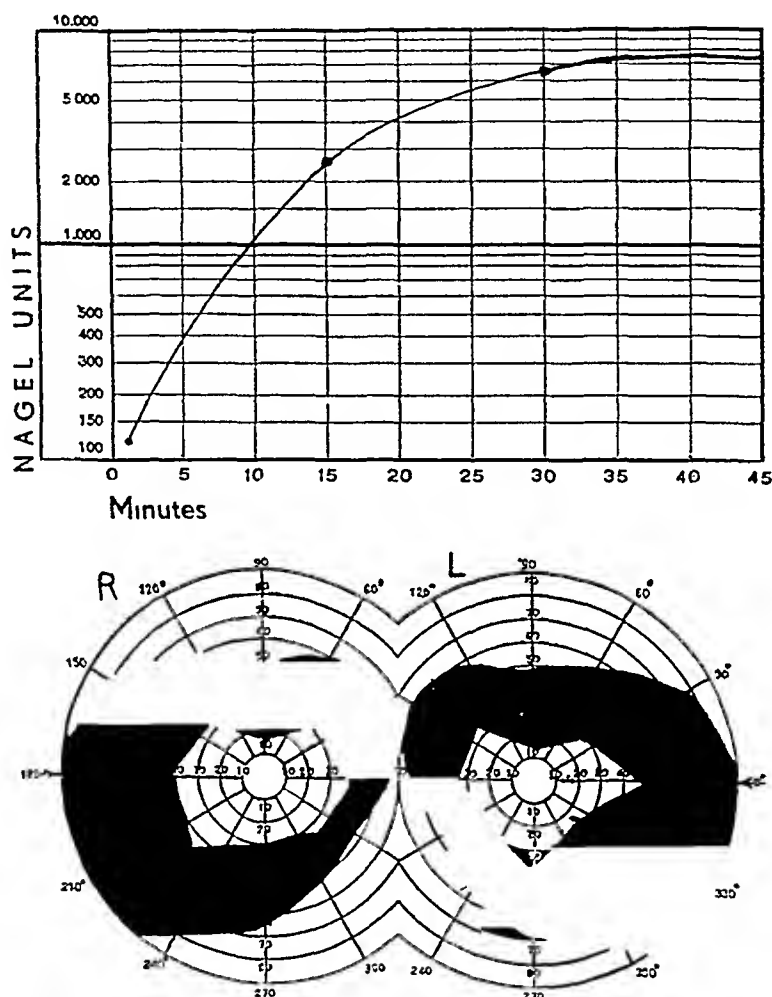


Fig 3—Dark adaptation readings taken Sept 14, 1944. Visual acuity was 20/40—2 in each eye without correction. With a correction (cycloplegic refraction) of -0.50 D sph -0.50 D cyl, axis 160 for the right eye and of -0.50 D sph -1.25 D cyl, axis 130 for the left eye, vision was 20/20 in each eye.

The fundusoscopic examination revealed primary pigmentary degeneration of the retina. The arteries were attenuated.

Below, visual fields taken at a distance of 1 meter with a 2 mm test object. Vision was 20/20 in each eye.

placed vertically on the sides. The Nagel adaptometer was then set so as to throw the light on this drum. One of the patient's eyes was anesthetized and a special contact lens placed over the cornea. The posterior surface of the lens was painted black and a small piece of radium paint

from a watch dial was secured on the center of the anterior surface. This permitted us to follow any movement of the opened eyes in a dark room. The patient was seated in front of the optokinetic drum and asked to open both eyes and gaze directly ahead. The drum was rotated slowly and the light from the adaptometer increased in intensity. The patient was told to report as soon as he could distinguish any moving objects. The patients showing an abnormal configuration curve of dark adaptation exhibited a nystagmus long before they reported seeing the drum. The patients with normal configuration curves of dark adaptation reported seeing the drum when the nystagmus developed.

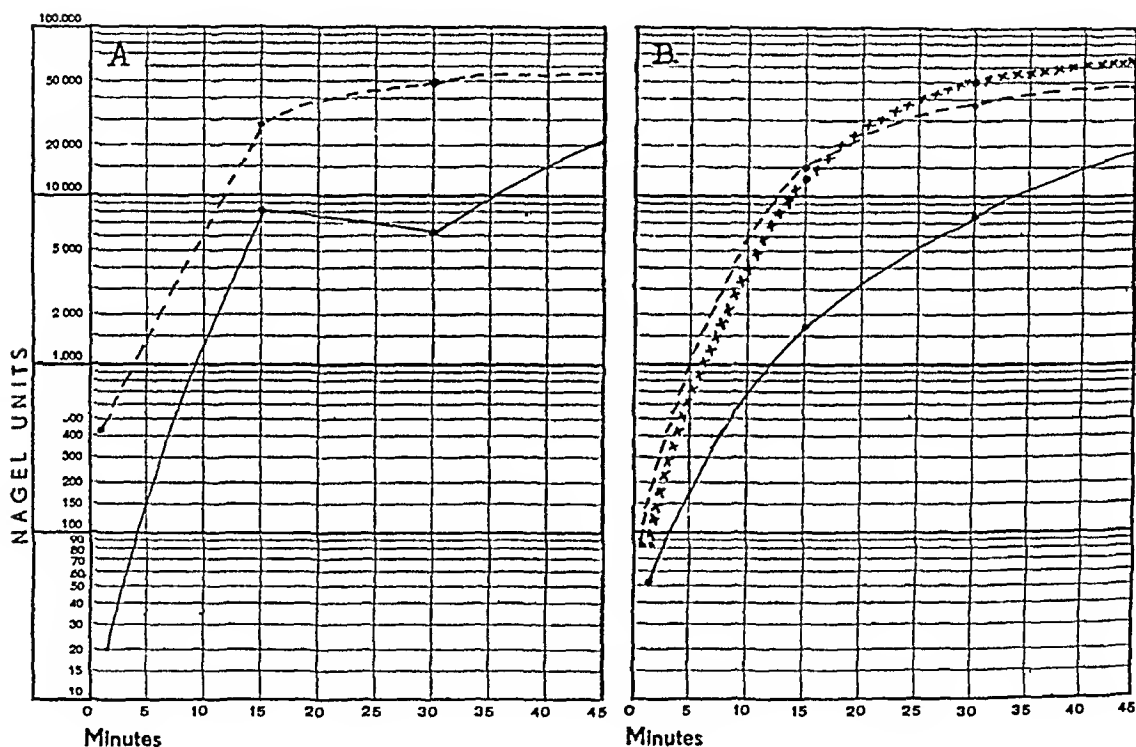


Fig 4—Dark adaptation readings for 2 patients (A) The patient gave evidence of malingering in tests with the optokinetic drum (solid line). The readings taken two hours later (broken line), after the patient was confronted with the seriousness of malingering, show a normal configuration curve and a normal final reading. Without correction visual acuity was 6/300 in the right eye and 20/30 in the left eye. After correction (cycloplegic refraction) of $+0.50$ D cyl, axis 90 for each eye, it was 6/200 in the right eye and 20/20 in the left eye.

(B) The patient had always had poor vision. Since being overseas, he had noticed poor night vision. This had become progressively worse. He was a gun pointer in an aircraft battery. The diagnosis was psychoneurosis. The solid line represents the readings taken August 1, the broken line, the readings taken August 10, after psychotherapy, and the line of crosses, the readings taken August 15, the day before the patient was returned to full duty.

Without correction visual acuity was 20/50 in each eye, with correction (cycloplegic refraction) of a $+0.50$ D sphere before each eye it was 20/50.

Once the evidence obtained by this test was sufficient, it was presented to the patient and the seriousness of malingering stressed. New determinations of dark adaptation were made, and for all 5 patients who initially showed abnormal configuration curves, normal configuration curves were obtained (fig 4A).

The 14 patients showing normal configuration curves of dark adaptation but low final readings were seen, both for diagnosis and for therapy, by members of the neuropsychiatric department, directed by Lieut Col Benjamin Boshes. A diagnosis of psychoneurosis was made in all cases. All 14 patients showed conspicuous improvement in final readings under psychotherapy, and there was a distinct improvement in associated hysterical manifestations, such as amblyopia and constriction of peripheral form fields (fig 4B).

These two groups were soon found to be anything but rigid. To understand this, it may be of interest to review the nature of both malingering and of psychoneurosis. In either condition the patient is attempting an escape from an undesirable situation. Both states are motivated by fear. Most of these patients were from combat organizations, where the fear of death was constant. A person with a desire to escape an unpleasant situation may consciously feign a physical defect and, unless apprehended, will continue to do so until the danger is removed. In the psychoneurotic patient the whole mechanism is at an unconscious level. It is interesting to note that many of these psychoneurotic patients had either poor vision or a high refractive error or were working at jobs in which their eyes were all-important. Thus, the unconscious was constantly being conditioned, and once the situation became intolerable escape was accomplished by a visual disability. Conditioning of an emotionally unstable person can be produced, as will be demonstrated later in this paper, simply by repeated examinations of the eyes. Therefore it is not surprising that these patients unconsciously sought escape through visual complaints.

Psychotherapy, which consists, first, of removing the undesirable situation and reassuring the patient and, second, of helping the patient gain insight into his condition by removing the motivating force, releases the mechanism whereby the dark adaptation is suppressed. The degree of this release depends on the intelligence and stability of the patient as much as it does on the psychotherapy.

Since both the malingering and the psychoneurosis are motivated by fear, unless the patient is fairly stable and has a strong desire to perform duty the prospect of returning to the unpleasant situation will produce a relapse. A malingerer who has been detected will ordinarily not attempt further escape by malingering, fearing the consequences. Examining his eyes has conditioned him, and often a psychoneurosis will

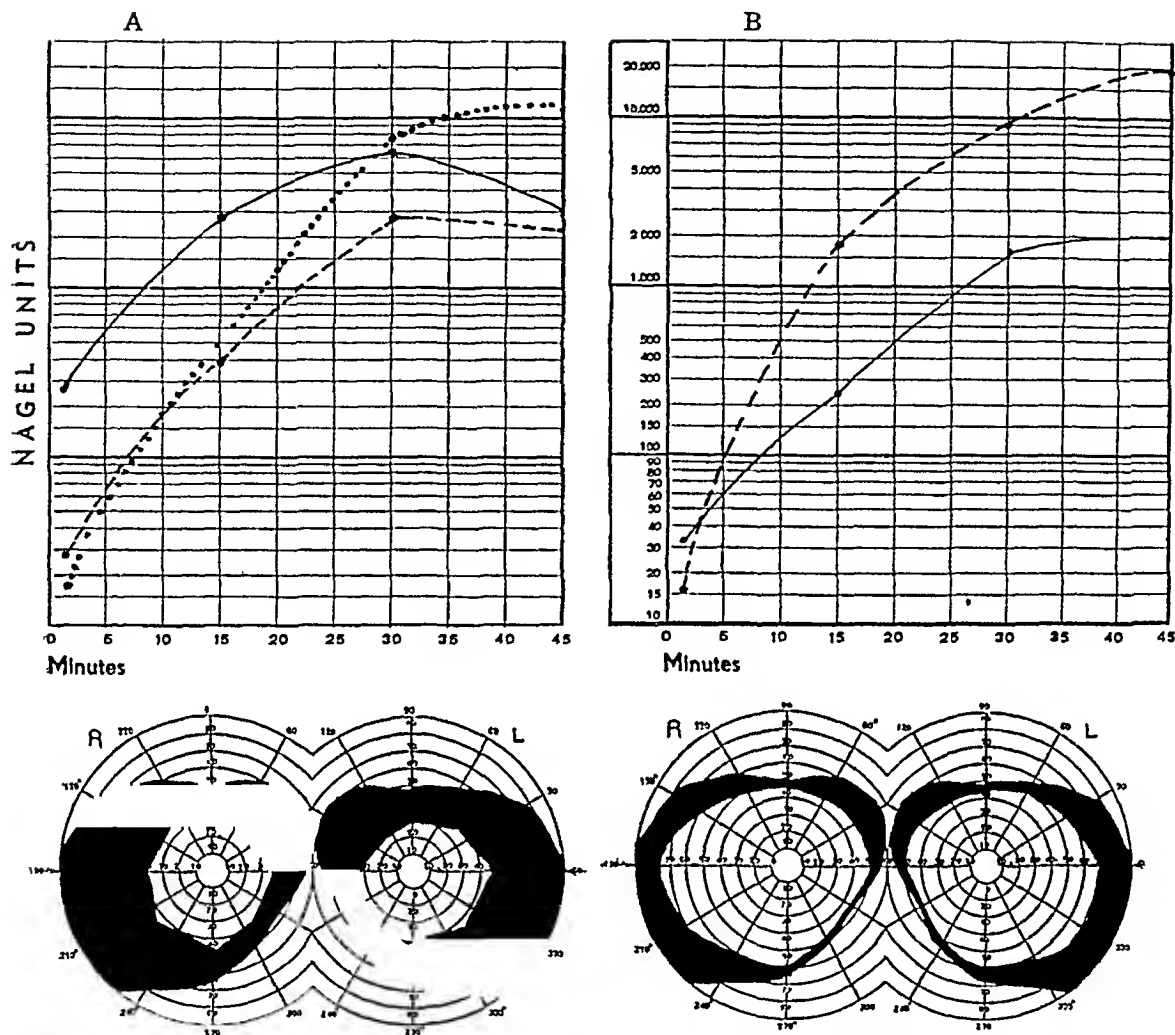


Fig 5—(A) The patient had been in the front lines one week and had become completely incapacitated because of poor vision. The solid line represents the original readings, taken July 20, showing an abnormal configuration curve with a low final reading, the broken line, the readings taken July 24 (the patient gave a positive test for malingering with the optokinetic drum), and the line of dots, the readings taken two hours later, after the patient was confronted with the seriousness of malingering, showing a normal configuration curve and a low final reading.

Below are the peripheral fields, taken before determinations of dark adaptation (July 24) were made.

Visual acuity was 20/200 in each eye without correction. With correction (cycloplegic refraction) of -3.50 D sph $+1.00$ D cyl axis 10 for the right eye and of -3.00 D sph $+0.75$ D cyl, axis 170 for the left eye, vision was 20/30 and 20/40, respectively.

(B) Continuation of studies shown in A. The patient was seen by members of the neuropsychiatric department, the diagnosis was psychoneurosis. The readings represented by the solid line were taken August 10. The patient had been told that he would return to duty. The broken line shows the readings taken August 15, five days after his admission to the neuropsychiatric ward and psychotherapy. The patient was still tense but showed improvement.

Below are the visual fields, taken August 15, after psychotherapy.

develop when he is faced with a return to duty. The psychoneurotic soldier once told he is well enough to return to duty may, in desperation, attempt malingering (fig 5)

PATIENTS WITH INFECTIOUS HEPATITIS

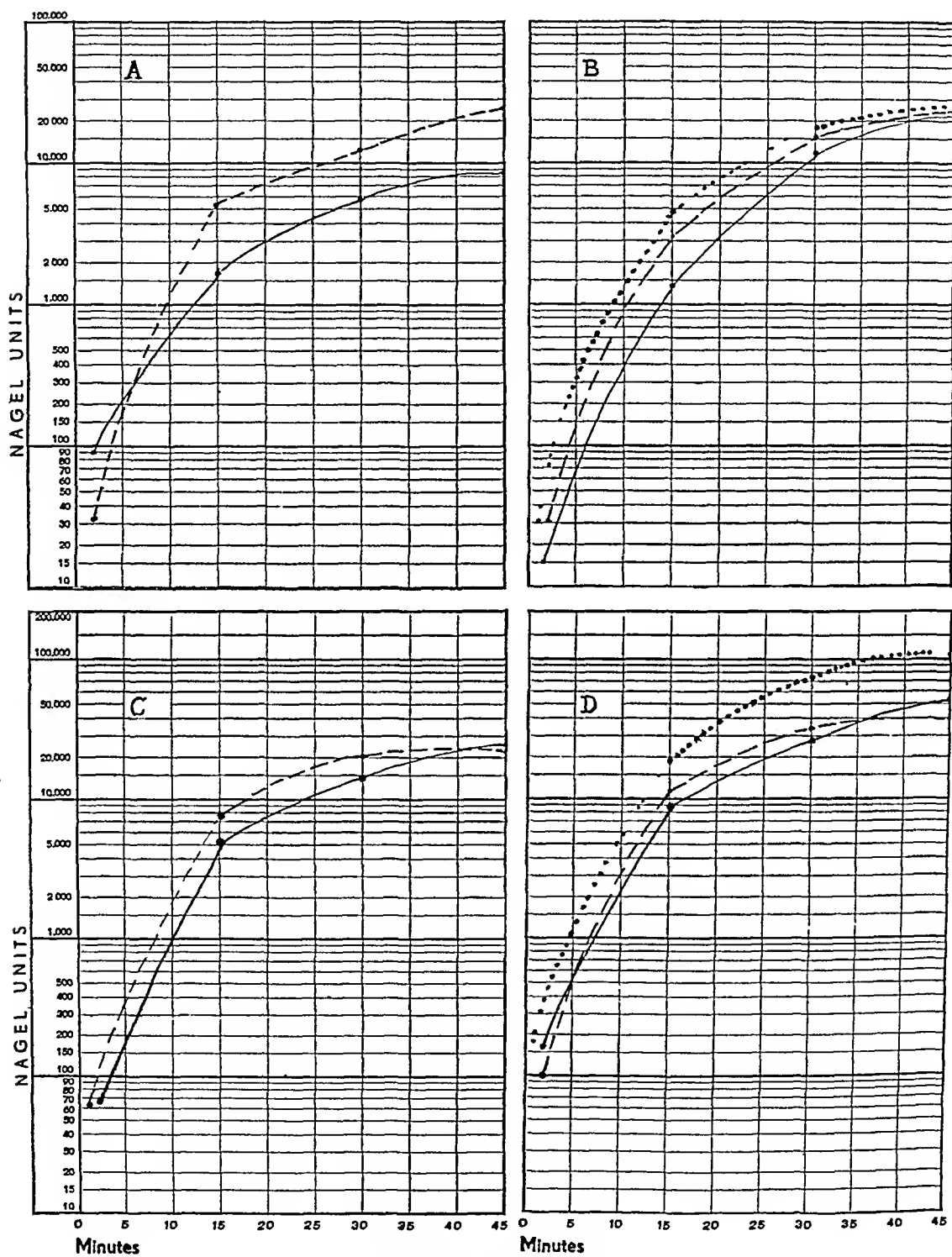
The remaining 13 patients examined were admitted to the hospital with a diagnosis of infectious hepatitis. Six of these patients had severe chronic infectious hepatitis, and another 6 patients were returned to full duty before fifteen weeks had elapsed after the onset of the disease. In the thirteenth patient, admitted with a condition diagnosed infectious hepatitis, medical work-up failed to show any evidence of hepatic disease. Initial dark adaptation readings for the 6 patients with severe chronic infectious hepatitis revealed that 4 had low final readings and normal configuration curves. The other 2 had normal readings, but after an exacerbation of the hepatitis both gave subnormal readings. All final readings in this group were less than 37,000 Nagel units.

Attention is called to the fact that on being hospitalized all patients with a diagnosis of infectious hepatitis were placed on a diet for patients with hepatitis, which is low in vitamin A and carotene. In addition, all had been given 2 multivitamin capsules a day, each containing 5,000 U S P units of vitamin A. The stools were not acholic in any case, so it can be assumed that absorption was adequate.

Three patients in the group with severe chronic infectious hepatitis and subnormal dark adaptation readings were given 40,000 U S P units of vitamin A orally per day, and within one week all showed decided improvement in dark adaptation. One of these 3 patients, who after one week of vitamin A therapy gave a final reading of 61,300 Nagel units, suffered an exacerbation of the hepatitis, during which time he was placed on a regimen of absolute rest in bed. After three weeks, when he was able to endure the trip to the University of Rome for examination, he gave a final reading of 26,000 Nagel units despite the fact that he had been given 40,000 units of vitamin A daily. Two patients had jaundice during hospitalization, and there was only a slight alteration in their dark adaptation readings, which were well within the range of error of the tests.

The 6 patients with mild hepatitis who returned to full duty before the fifteenth week after onset of the disease had normal dark adaptation curves. These patients were given 40,000 U S P units of vitamin A daily, without any decided increase in dark adaptation. Only 1 patient of this group showed any appreciable change after vitamin A therapy (fig 7).

The 1 patient who was admitted with a condition diagnosed as infectious hepatitis and in whom no hepatic disease could be demonstrated, on initial examination gave a final reading of 58,000 Nagel units.



(See legend on opposite page)

The visual fields were normal, and visual acuity was normal. Ophthalmologic examination revealed no pathologic condition. Forty thousand units of vitamin A was administered daily. Two weeks later, on reexamination, the final dark adaptation reading was 35,000 Nagel units. Neuropsychiatric consultation revealed an existing psychoneurosis. His complaints of upper abdominal distress were at this time secondary to vague visual complaints.

No pathologic condition of the eyes was found in the group of 12 patients with a condition diagnosed as infectious hepatitis. In 1 patient examination with the slit lamp showed prominent corneal nerves, and in a rough sensitivity test he was believed to have mild corneal anesthesia.

Abnormal results with the cephalin flocculation and sulfobromophthalein sodium tests were obtained from all patients during hospitalization. All but 3 patients presented an increased icterus index at some time during their stay in the hospital. These 3 patients had a history of dark urine and jaundice previous to admission.

EXPLANATION OF PLATE

Fig 6—(A, B and C) Configuration curves for a patient whose history dates back to May 1944, when loss of appetite, malaise and generalized aches and pains developed. He was wounded and hospitalized. He returned to duty June 1944 and noticed for the first time that he was unable to see the white tape at night used by the engineers to mark off mine fields. For two weeks he was led around at night by a sergeant. He was admitted to the hospital early in July 1944, for nausea, vomiting and elevated temperature. The diagnosis was hepatitis.

Visual acuity without correction was 6/200 in the right eye and 4/200 in the left eye. After cycloplegic refraction, a correction of +2.25 D sph \ominus +0.75 D cyl, axis 120 for the right eye and of -3.00 D sph \ominus +1.50 D cyl, axis 80 for the left eye gave vision of 20/50 in each eye.

(A) The readings taken August 1 are shown by the solid line, those taken August 8, after administration of 40,000 units of vitamin A daily, by a broken line.

(B) The solid line represents the readings after jaundice had developed. The patient had been receiving 40,000 units of vitamin A daily. The broken line represents the readings taken August 24, after the patient had been receiving 40,000 units of vitamin A daily. The jaundice was still present. The line of dots shows the reading taken August 31, while he was receiving 40,000 units of vitamin A daily. The icterus index was 4.

(C) The readings shown by a solid line were taken September 7, while the patient was receiving 40,000 units of vitamin A daily. The icterus index was normal.

The reading shown by a broken line was taken September 14, while the patient was receiving 40,000 units of vitamin A daily. The icterus index was normal.

(D) Dark adaptation readings for another patient, with onset of hepatitis twelve weeks prior to the first reading. The results of the hepatic function tests were abnormal. The liver was tender and palpable 3 fingerbreadths below the costal margin. Neuropsychiatric consultation revealed nothing abnormal.

The readings represented by a solid line were taken August 10; those shown by a broken line, August 17, after the patient had received vitamin A, 40,000 units for three days, and those shown by a line of dots, August 24, while the patient was receiving 40,000 units of vitamin A daily. No clinical improvement was apparent. The results of the hepatic function tests remained abnormal.

Although the patients with chronic infectious hepatitis showed subnormal dark adaptation, corneal changes and evidence of vitamin A deficiency were not noticed. Although 1 patient had prominent corneal nerves, such a finding is not unusual. Gifford³ stated that when night blindness affects adults as a result of vitamin A deficiency it is usually noticed before corneal changes occur.

Dark adaptation is somewhat dependent on the level of vitamin A in the plasma, the substance being transferred by this route from the

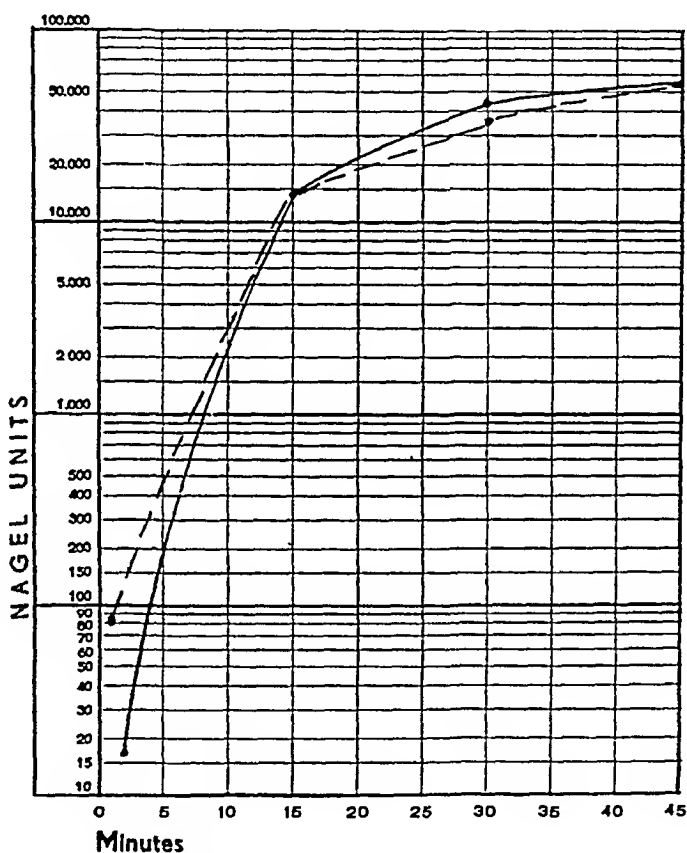


Fig 7—The corneal nerves were prominent. Corneal sensibility was decreased with the cotton test. The onset of hepatitis was July 20. Jaundice was noted July 27. There was no jaundice at the time of the initial reading, August 24 (solid line), and the icterus index was 2. The liver was tender and palpable 2 fingerbreadths below the costal margin, and the results of hepatic function tests were abnormal.

The reading on September 14 (broken line) was taken after the patient had been receiving 40,000 units of vitamin A daily for sixteen days. The hepatic function tests showed improvement.

Visual acuity was 20/70 without correction. Cycloplegic refraction gave a correction of -1.50 D sph \cap $+1.25$ D cyl, axis 180 for the right eye and -2.00 D sph \cap $+1.75$ D cyl, axis 180 for the left eye.

³ Gifford, S. R. Textbook of Ophthalmology, ed 2, Philadelphia, W. B. Saunders Company, 1941.

storage depots in the liver to the pigmented epithelium of the retina, where it is utilized in the resynthesis of rhodopsin, the photosensitive pigment in the rods

Recent work by Popper and associates⁴ has shown that there is no relation between the level of vitamin A in the plasma and that in the liver in patients with hepatic disease. They often found a plasma level of zero in patients with hepatic disease, but repeated examinations failed to show an absence of vitamin A in the human liver. They stated the belief that a vitamin A deficiency may be caused by a deficiency in release of vitamin A from the liver rather than by a depletion of the storage depots. They proved this statement by vitamin A fluorescence studies and by comparison of vitamin A concentrations in the plasma and in the liver. Patients with hepatic disease showed an abnormal distribution of vitamin A in the liver cells. Vitamin A fluorescence of the hepatic tissue closely paralleled the vitamin A concentration in the liver, but only in cases in which the vitamin A concentration in the plasma was high did it parallel the concentration in the liver. In patients with a low vitamin A level in the plasma and an abnormal vitamin A distribution in the liver, the plasma level could be increased by the administration of massive doses of vitamin A orally.

In our 6 patients in whom the hepatitis was mild and did not become chronic we may assume that the parenchymal damage was not sufficient to affect the liver-plasma relationship of vitamin A concentration seriously, since none showed a marked improvement in light sensitivity after receiving 40,000 units of vitamin A daily. In the 6 patients with severe hepatitis the parenchymal damage can be assumed to have been severe enough to have caused an abnormal distribution of vitamin A and a deficiency in the release of vitamin A from the liver. After oral administration of vitamin A these patients showed a marked increase in light sensitivity, manifested by improved dark adaptation readings.

That an acute exacerbation of the hepatitis could further depress the vitamin A level in the plasma is demonstrated in the case of 1 patient previously mentioned, in whom after an exacerbation dark adaptation was decreased despite the administration of 40,000 units of vitamin A daily. This points to a relationship between the degree of damage to the liver and the depression of release of vitamin A into the plasma. It may also account for the fact that 1 of the patients showing notable improvement in dark adaptation with vitamin A therapy failed to give a normal final reading despite having received 40,000 units of vitamin A daily for eight weeks. The highest final reading for this patient was

⁴ Popper, H., Steigmann, F., Meyer, K. A., and Zevin, S. S. Relation Between Hepatic and Plasma Concentrations of Vitamin A in Human Beings. *Arch Int Med* 72:439 (Oct) 1943.

26,000 Nagel units, obtained after one week of vitamin A therapy and maintained for seven weeks. It would be interesting to know what a larger dose of vitamin A would have accomplished. Popper and associates reported giving their patients 75,000 units of vitamin A daily.

It seems unlikely that jaundice per se affects regeneration of visual purple, since 2 of our patients showed no appreciable change in dark adaptation when jaundice developed during the course of the disease.

The patient who was admitted with a diagnosis of hepatitis, complaining of upper abdominal distress, and later was proved to be psychoneurotic is of interest. His escape was blocked by its being proved that he had no hepatic disease. When he was faced with returning to the front, there developed night blindness and vague visual complaints. Thus, determination of dark adaptation and ocular examinations conditioned the patient, and, faced with the return to an undesirable situation, he unconsciously acquired an ocular disability.

SUMMARY

Sixty-six patients were examined with a Nagel adaptometer for determination of dark adaptation. Careful ophthalmologic examinations were made, and neuropsychiatric consultation was secured when indicated.

Thirty-nine patients of the group complained of moderate to extreme night blindness. Fourteen had no ocular complaints, and 13 were patients with hepatitis.

Of the 14 patients with no ocular complaints, all showed normal adaptation curves, and final readings after forty-five minutes ranged from 50,000 to 150,000 Nagel units. None had a corrected central vision of less than 20/20, and with homatropine cycloplegia none had a refractive error of more than 1.00 D.

Of the 39 patients complaining of night blindness, 5 with moderate complaints showed normal dark adaptation, and 3 of these had more than —1.50 D of astigmatism. For 6 others with normal readings but severe complaints detailed histories revealed some incident that had caused the patient to believe that his night vision was inadequate. Of this group, 3 had moderate myopic astigmatism.

The remaining 28 of the 39 patients admitted complaining of night blindness had initial low readings for dark adaptation. No cause for this could be found in 5 patients, and these men were considered to have true simple hemeralopia, 4 had a pathologic condition of the fundus, 5 patients proved to be malingerers, and 14 were psychoneurotic.

Of the 19 patients who were malingerers or psychoneurotic, 11 had corrected vision of 20/40 or less, and 12 had refractive errors of above 1.50 D.

A test for malingering is described which utilizes the principle of optokinetic nystagmus

Of 13 patients examined who were admitted to the hospital with a diagnosis of infectious hepatitis, 1 proved to be psychoneurotic

Six patients with chronic disease of the liver showed subnormal dark adaptation. Three of these persons were given oral vitamin A therapy, with pronounced improvement

Six patients with infectious hepatitis, whose disease did not become chronic and whose hospitalization did not exceed fifteen weeks, showed normal dark adaptation curves. Little or no improvement in dark adaptation was noted in this group when massive doses of vitamin A were given

Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

Conjunctiva

HISTOLOGIC STUDY OF PEMPHIGUS OF THE CONJUNCTIVA D D AQUILA
DE CASTANE DECOUD, *An argent de oftal* 5:44 (April-June)
1944

Few histologic studies of this condition have been reported, and all were made at advanced stages of the disease or at a cicatricial stage

The author gives the following resume of the histologic changes in a case in which the disease was not advanced "The conjunctiva was much thickened throughout The epithelium showed hyperplastic lesions and epidermal metaplasia The tissue proper presented conspicuous changes edema, myxoid appearance, angiohyperplastic granulomas, chronic inflammatory tissue (infiltration of plasma cells and lymphocytes) and conspicuous sclerosis The meibomian glands showed cystic degeneration and lipoplastic granulomas"

The article is illustrated

H F CARRASQUILLO

Experimental Pathology

THE SUDDEN DEATH OF MICE INJECTED INTRAORBITALLY WITH
MINUTE QUANTITIES OF SESAME OIL F H J FIGGE, *Proc
Soc Exper Biol & Med* 57:24 (Oct) 1944

In the course of an experiment designed to test the sensitivity of the harderian gland to induction of tumors, about 50 mice were given injections of methylcholanthrene in 0.05 cc of sesame oil All these mice died within one to two minutes after the injection Animals atropinized by intraperitoneal injection prior to the intraorbital injection of sesame oil survived the latter and continued to live The author concludes that the oculocardiac reflex was responsible for the death of the nonatropinized animals

P C KRONFELD

General

OPHTHALMOLOGY IN LAGOS 1943 R WALKINGSHAW, *Brit J Ophth*
29:221 (May) 1945

A classification is given of the ocular conditions seen in the ophthalmic division of the African clinic at Lagos during 1943 This is followed by comments on the various disorders classified To avoid conveying trachoma to other patients, and for other reasons a special clinic was held in the afternoon for treatment of patients with this disorder Not a single case of syphilitic interstitial keratitis was seen Cyclitis is the principal disease of the uveal tract in Lagos A striking proportion of cases of well established unilateral cataract was observed in patients aged 30 years and over None was of traumatic origin

Primary atrophy of the optic nerve is extremely common and is considered to be due to avitaminosis in the great majority of cases. Only 1 case of acute glaucoma was seen, the attack was superimposed on chronic glaucoma. Chronic glaucoma is comparatively common and occurs in comparatively young people, starting at the age of 20 and reaching its maximum at about the age of 35. Diseases due to dietary deficiencies, with the exception of vitamin A deficiencies, are many and varied.

W ZENTMAYER

Hygiene, Sociology, Education and History

STATUS OF COMPENSATION FOR OCULAR INJURIES IN THE UNITED STATES M DAVIDSON, *Am J Ophth* 28: 856 (Aug) 1945

Davidson remarks the wide diversity of standards of compensation for an industrially damaged eye in the different states. He discusses various phases of compensation and concludes that the method proposed by the committee of the American Medical Association offers the most acceptable basis of securing uniformity.

W S REESE

Injuries

PROBLEMS BROUGHT ABOUT BY THE TOLERANCE OF INTRAOCULAR AND ORBITAL FOREIGN BODIES J M VILA ORTIZ, *Arch de oftal de Buenos Aires* 19: 41 (Jan) 1944

In the author's statistics there is a rather high incidence of cases (4 out of 26) in which foreign bodies were tolerated. In 1 case the foreign body was tolerated for seventeen years, in 1 case for four years and in another for one and a half years.

The author gives his criteria as to what should be done in such cases.

H F CARRASQUILLO

TREPHINING OF THE CORNEA OF CASES OF TRAUMA OF THE EYE P V ARKHANGELSKY, *Vestnik oftal* 23: 23, 1944

Arkhangelsky used trephination of the cornea for removal of foreign bodies from the anterior chamber in 10 cases, he also employed it in 2 cases of cataract in which there was no anterior chamber. The histories in 4 cases are given. In 1 of these, a woman physician aged 35 had injured her eye with glass. Two attempts to remove the glass from the anterior chamber by means of the usual incision with the keratome were unsuccessful. An enucleation was considered, but a third attempt was made with a trephine (Filatov's), and the piece of glass was removed through the trephine hole. A thin round scar usually forms at the site of the trephine. This operation was suggested by Haab in 1922.

O SITCHEVSKA

Lens

EXPERIMENTAL AND CLINICAL STUDIES ON CERTAIN SAFETY FACTORS IN CLOSURE OF CATARACT INCISIONS A C HILDING, *Am J Ophth* 28: 871 (Aug) 1945

Hilding stresses the importance of corneal flaccidity and scleral resilience in preventing prolapse of the iris and feels that sutures should

be so placed after cataract extraction that if the wound gapes post-operatively it will do so at a predetermined spot. A tiny peripheral iridectomy should then be made in this meridian. He describes two operations based on these principles, and their results.

W S REESE

AN UNUSUAL TYPE OF ANTERIOR TRAUMATIC CAPSULAR CATARACT
E ROSEN, Brit J Ophth 29: 373 (July) 1945

One month after a penetrating injury of the cornea with injury to the lens, there was a V-shaped, through and through scar about the center of the cornea. Several folds radiated from the main scarred mass of the anterior capsular cataract, suggesting that the anterior capsule was thrown into multiple waves. It is characteristic of "glass membranes" to become wrinkled, as is seen in Descemet's membrane. One would expect such waves to be more common with anterior capsular cataract. On the other hand, the folds may be the result of radiations from an indented wound, with epithelial proliferation of the capsule of the lens and subsequent shrinkage with scar contraction and formation of striae.

W ZENTMAYER

Lids

SUBCUTANEOUS SPLITTING OF THE LID IN THE OPERATIVE TREATMENT
OF SENILE ECTROPION H LYTTON, Brit J Ophth 29: 378
(July) 1945

This operation avoids the splitting of the lid margins. With an angular scissors, the skin-muscle layer of the lid is separated from the tarsoconjunctival layer by inserting the blades of the scissors in an incision made on a line with the outer canthus. The separation is extended up to immediately beneath the margin of the lid, keeping close to the anterior surface of the tarsus. Two mattress sutures are inserted in the anterior layer of the lid near the lid margin. These sutures are used to lift the skin. The tarsal plate is drawn down with two Snellen sutures. The lateral incision is completed to the excision of a Szymanowski triangle. The Snellen sutures are tied in the usual manner, and the lifting sutures are fastened above the brow with strips of adhesive plasters.

W ZENTMAYER

Neurology

THE OCULAR MANIFESTATIONS OF HYSTERIA IN RELATION TO FLYING
R IRONSIDES and I R C BATCHELOR, Brit J Ophth 29: 88 (Feb)
1945

This paper, which does not lend itself to satisfactory abstraction, deals mainly with hysteria, in particular with a series of 40 cases of hysteria in flyers.

The symptoms presented by these patients are similar to those complained of by patients with organic ocular defects and diseases and are out of proportion to any ocular disability which may be present.

The subject is considered under the headings of visual aberrations experienced by normal aircrews, a comparison of cases of hysteria and cases of affective disorder, the ocular symptoms of hysteria, the objec-

tive results of examination, the relation of neurotic manifestations to inherent ocular defects, factors predisposing to the development of ocular symptoms and differential diagnosis

W ZENTMAYER

TUMORS OF THE CEREBELLOPONTILE ANGLE E SALGADO BENAVIDES,
Arch Soc oftal hispano-am 4:75 (Jan-Feb) 1944

After an extensive discussion of the neurologic symptoms and ocular signs associated with tumors of the cerebellopontile angle, the author arrives at the following conclusions

In the present state of knowledge the ophthalmologist cannot with certainty contribute to the differentiation of a neuroma of the acoustic nerve and other tumors of the cerebellopontile angle. The state of cranial hypertension produces a series of changes in the fundus oculi, of which papilledema is the typical one. Paralysis of the sixth nerve, of frequent occurrence, has little value in localization of the growth. It may be evidence of intracranial hypertension, or it may be produced by infiltration of the tumor tissue into its nucleus or by pressure on its root, which has a long course. The homolateral loss of the corneal reflex, always present with tumors of the cerebellopontile angle, is of value as a localizing symptom, since it makes its appearance early as a sign of involvement of the trigeminal nerve.

H F CARRASQUILLO

OPTIC NEURITIS COMPLICATING POLIOMYELITIS CLINICAL AND
EXPERIMENTAL STUDY R BERGMAN, K O GRANSTROM and
J H MAGNUSSON, Acta pædiat 30:176 (Dec 23) 1942

Bergman and his associates report the case of a girl aged 9 years who presented the clinical picture of acute meningoencephalitis, with paresis of the respiratory muscles, paresis of the right arm and right leg, paresis of the right facial nerve of central type, paresis of the palate and slight stiffness of the neck. The patient was placed in the respirator for twenty-two hours, and all the signs of paresis disappeared. Double optic neuritis was observed one month later. A diagnosis of poliomyelitis was made because at the time of the patient's admission to the hospital an epidemic of poliomyelitis was in progress, many cases of which presented the same clinical picture as that in the case reported. The diagnosis was clarified by an experimental investigation. Intraperitoneal and cerebral injections of etherized suspensions (50 and 0.5 cc, respectively) of a fecal specimen taken the day after the patient's admission to the hospital were given to a *Macacus rhesus* monkey. Twenty-seven days later the monkey was killed. While alive it did not present any symptoms of paralysis. Hyperemia of the axillary, inguinal and mesenteric lymph nodes was demonstrated at necropsy. Perivascular mononuclear meningitis was revealed on microscopic examination of the central nervous system. A massive perivascular cellular infiltration characteristic of experimental poliomyelitis was found beneath the cortex of the brain, in the walls of the lateral ventricles and in the area adjacent to the aqueduct of Sylvius. There were no such changes in the gray substance of the spinal cord, but a focus of mononuclear cells was found in the white

substance of the upper dorsal portion of the spinal cord. A few typical neuronophages were observed in the ventral wall of the aqueduct. Three weeks later intraperitoneal and cerebral injections of an emulsion of the brain substance of the animal were given to a second *Macacus rhesus* monkey. Examination of this monkey revealed no changes while the animal was alive, but hyperemia and enlargement of the inguinal and axillary lymph nodes were demonstrated likewise at necropsy. Occasional perivascular infiltrations were found in the walls of the lateral ventricles and the floor of the fourth ventricle. Perivascular meningitis of the thoracic portion of the spinal cord, characteristic of poliomyelitis, was revealed. On the basis of these observations, it was considered that the optic neuritis was caused by the same infection.

J A M A (W ZENTMAYER)

Ocular Muscles

USE OF BISMUTH SUBSALICYLATE IN CURE OF SYPHILITIC INTERNAL OPHTHALMOPLÉGIA. N. PREZIDIO DE FIGUEIREDO, *Rev. brasil. de oftal.* 3:3 (Sept.) 1944.

A patient aged 25 had complained of visual disturbances in the right eye for a year. The iris and cornea were normal. The pupil was dilated, the direct and indirect pupillary and accommodative reflexes were absent. The fundus was normal. A diagnosis of internal ophthalmoplegia was made. An infected tooth was removed, without improvement. The Kahn reaction of the blood was positive. Injections of 1 cc. of bismuth subsalicylate once a week were given intramuscularly. At the end of three months, four days after the tenth injection, the Kahn reaction was negative. Visual acuity and accommodation were normal in the right eye. The pupillary diameter and reflexes were normal.

The author believes that the rarity of cases of this disease is due to the fact that involvement of the neuromuscular apparatus of the eye in the majority of cases of syphilitic origin is slow and the patient delays consulting an oculist until diplopia appears.

The use of bismuth subsalicylate, the author believes, would be efficacious in many cases.

M. E. ALVARO

COMMENTS ON STRABISMUS. BARBOSA DA LUZ, *Rev. brasil. de oftal.* 3:13 (Sept.) 1944.

Bimocular vision can occur only under the following conditions: (1) good fixation with exact projection in each eye, alone and simultaneously with the other eye, (2) visual acuity of approximate equality in the two eyes, (3) similar form and size of images received by the fovea, (4) integrity of the neuromotor-muscular mechanism of each eye, alone and associated with the other eye, (5) perfect sensorial correspondence of the symmetric points in the two retinas, and (6) cerebral coordinating center able to merge the two monocular images. These conditions are discussed in detail. The importance of a careful examination is stressed in every case of squint in order to determine the cause. Nugent's paper on 134 cases of strabismus

(*Am J Ophth* 23:68 [Jan] 1940) and the report by Berens, Elliot and Sobacke of 324 cases of strabismus (*Am J Ophth* 24:1418 [Dec] 1941) are summarized in a chart. A bibliography is included.

M. E. ALVARO

Operations

TECHNIC OF ENUCLEATION OF THE EYE V. P. FILATOV, *Vestnik oftal* 23:3, 1944

Filatov used Trillof's method of enucleation (with modification), i. e. "from back forward". The optic nerve is severed immediately after section of the internal rectus muscle, then all the other muscles and ligaments are cut. Filatov finds that this type of enucleation shortens the time of the operation and simplifies the problem created by the formation of scar tissue and adhesions after war injuries of the eyeball. The lids must be widely separated, and the optic nerve should be turned outward as much as possible, instead of being stretched forward.

O. SITCHEVSKA

Refraction and Accommodation

MYOPIA (A STATISTICAL ANALYSIS) K. N. SHUKLA, *Indian J Ophth* 6:7 (April) 1945

Shukla stated that this analysis is in no way a survey of the state of refraction of the population in general but can be taken to represent only that section of the community (Lucknow) which stands in need of glasses for the improvement of vision or relief from symptoms of asthenopia. The distribution of persons with myopia and hyperopia at various ages is as follows. The number of myopic persons is highest between the ages of 20 and 25 years, the rise is most striking between the ages of 10 and 20 years, the fall after the age of 25 is equally sharp, from the age of 35 on the figure remains practically constant. The curve showing the distribution for hyperopia behaves exactly like that for myopia until the age of 35 years, after which, unlike the curve for myopia, it rises again.

Caste has not much influence in the incidence of myopia. Myopia is commoner in males than in females. The incidence is very high in private patients.

W. ZENTMAYER

Trachoma

TREATMENT OF TRACHOMA, WITH SPECIAL REFERENCE TO LOCAL SULPHONAMIDE THERAPY A. SORSBY, *Brit J Ophth* 29:98 (Feb) 1945

The basis of this report is the treatment of a series of 200 patients under ideal conditions for continuous observation, which allowed a certain amount of experimentation in treatment. The work is summarized as follows. Considerable departure from the classic methods of treatment is now possible in trachoma. The time-honored copper sulfate stick has no place in present day therapy. Expression and the local use of sulfacetimide can in themselves bring about a clinical cure.

of trachoma Valuable supplementary measures are general sulfonamide therapy, local application of saturated solution of quinine bisulfate, mercury bichloride, 0.5 to 2 per cent in glycerin, and subconjunctival injections of Trachocid (a proprietary preparation said to contain bee venom) Modern therapy cuts drastically the period of infectivity and the duration of treatment

W ZENTMAYER

SULFANILAMIDE IN TREATMENT OF TRACHOMA S DE ALMEIDA TOLEDO, *Arq brasil de oftal* 7: 68 (April) 1944

De Almeida Toledo reports good results from the oral administration of sulfanilamide to two groups of patients, 4,741 and 49,891 respectively, from several of the trachoma and public health centers of Rio de Janeiro and other states of Brazil in 1943 The drug was administered to children and adults in daily doses of 0.5 Gm for each 15 Kg of body weight for twenty consecutive days, after which the therapy was discontinued if the patient was cured Cure was pronounced when examination of the eyes for three consecutive months with intervals of one month between examinations gave negative results for trachoma Sulfanilamide therapy was associated in all cases with administration of one or more of the following substances sodium bicarbonate in water, nicotinic acid alone or in association with either ascorbic acid or a preparation of calcium chloride and gentian violet medicinal, aminoacetic acid and liver extract A liberal intake of water (no less than 2 liters a day) is necessary Sulfanilamide therapy is a harmless and reliable treatment of trachoma

W ZENTMAYER

Tumors

A NOTE ON THE ROSETTES, NATURE AND NOMENCLATURE OF "GLIOMA RETINAE" E WOLFF, *Brit J Ophth* 28: 448 (Sept) 1944

There can be little doubt that rosettes are derived from fetal rod and cone cells Wolff has come to the conclusion that glioma of the retina arises from all the elements of the primitive nuclear zone (at an early stage the retina consists of a single nuclear zone and the marginal, almost non-nucleated, zone of His) except probably the ganglion cells destined to form the inner and outer nuclear layers and the glia To account for differences between one growth of this type and another—why, for instance, some tumors consist almost entirely of rosettes while in others none can be found—one would suggest that the relative number of the original constituents may vary Wolff thinks that the best term to use in place of "glioma retinae" is "retinoblastoma," suggested by Verhoeff in 1924 and adopted by the American Ophthalmological Society in 1926, but it must be made synonymous, as Verhoeff intended, with the classic glioma retinae

W ZENTMAYER

Vitreous

TERSON'S SYNDROME A PRIOR GUILLEM, *Arch Soc oftal hispano- am* 4: 408 (May-June) 1944

This rare syndrome, first described by Terson in 1900, is characterized by a hematoma of the vitreous body and spontaneous intracranial hemorrhage

Prior Guillem reports a case in a woman aged 63 who had had an apoplectic attack which produced left hemiplegia and sudden loss of vision in the right eye. On examination the patient presented hemiplegia of the left side, paralysis of the inferior branch of the facial nerve on the same side and incomplete palpebral ptosis on the right side. Her blood pressure was 195 systolic and 110 diastolic. There were paralysis of the oculomotor nerve and a massive hemorrhage in the vitreous. The retinal arterial pressure was 90 systolic and 35 diastolic. The Wassermann reaction of the serum was positive.

The author is in accord with Terson that this syndrome is produced by a subarachnoid hemorrhage, which gives rise to a venous stasis, producing in this way the ocular lesion.

H. F. CARRASQUILLO

Society Transactions

EDITED BY DR W L BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

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Dec 17, 1945

Adult Malformations of Embryonic Origin DR A L KORNZWEIG

The causative factors in malformations of the eye which may occur during embryonic life are the toxins derived from maternal disease, actual infections of the eye with organisms which can pass through the placental barrier, retardation and arrest in development for reasons that are unknown and germinal factors

Slides were shown which covered the development of the eye from the 55 mm stage to the fifth month. The time and the possible mechanism for the development of anomalies were demonstrated at the different stages. Of the anomalies discussed, the chief were those associated with disturbances around the fetal fissure, which account for microphthalmos, with and without cyst formation, and typical colobomas of the choroid, iris, ciliary body and optic nerve. The anomalies associated with the embryonic circulation of the lens were demonstrated. These included the remnants of the hyaloid artery from the optic nerve to the lens, which might be present and the pupillary membrane in front of the lens.

The development of the anterior chamber and the possible anomalies due to defects in differentiation of the angle of the iris were shown. Chief among these is congenital hydrophthalmos, the different types of typical coloboma of the iris and aniridia. The development of the lens was illustrated, and the time of the possible occurrence of opacities in the lens was noted.

The other anomalies shown were dermoids of the cornea, gliosis of the optic disk, remnants of Bergmeister's papilla and some anomalies of the lids.

Keratoconjunctivitis Sicca—a Sequela of Purulent Erythema Multiforme Exudativum (Stevens-Johnson Disease): Report of a Case DR JOHN M RICHARDS

Severe erythema multiforme exudativum is a rare disease of acute onset, characterized by fever, conjunctivitis, stomatitis and cutaneous lesions. Its course, although seldom fatal, is protracted, and its ocular sequelae often result in partial or total loss of vision. The cause is obscure, and pathologic findings are nonspecific except in the phytopharmacologic test.

A case of the purulent conjunctival form of erythema multiforme exudativum (Stevens-Johnson disease) followed by keratoconjunctivitis sicca was presented. The ocular lesions and symptoms were typically severe, resulting in loss of the right eye and in decreased vision in the left eye. Chemotherapeutic measures were employed as prophylaxis against secondary infection, and mechanical palliative measures were used locally, including wearing of special contact lenses. Roentgen therapy of the cornea was employed to decrease infiltration and vascularization. The condition was differentiated from pemphigus.

DISCUSSION

DR NATHAN SOBEL. I should like to emphasize the rarity of the Stevens-Johnson syndrome. I have encountered many cases of erythema multiforme bullosum but have never seen the cornea involved before. I understand this syndrome is much more common in children than in adults. Recently I heard of a case of the condition in a child at the Morrisania City Hospital, in that case the eye cleared up completely, and vision was restored.

With respect to the differentiation from pemphigus, the points Dr Richards made are correct, but the Pels-Macht test has been given up by dermatologists as having no value.

DR A. L. KORNZWEIG. I think the term keratoconjunctivitis sicca is used to indicate the condition associated with a definite syndrome, known as Sjogren's syndrome. Other types of keratoconjunctivitis with dryness, secondary to other causes, should be so designated.

Reconstruction of the Eyelids and of the Socket: Report of a Case

DR BERNARD FREAD

A middle-aged man, while drilling, was hit in the left eye with an unexploded stick of dynamite in January 1942. The left eyeball was ruptured and later enucleated. The deformity of the eyelids was considerable, including ectropion of the left lower lid and obliteration of the left socket. A sinus extended from the inner corner of the left eyebrow to the nose, and there were numerous fractures of the nasal bone.

A plastic surgeon repaired the nasal deformity with a cartilage implant, and the sinus was closed in April 1944. The ophthalmic condition was corrected in three operations. At the first operation, in May 1944, extensive bands of scar tissue were excised, the colobomas of the lid repaired and the margins of the lids aligned. At the second operation, in June 1944, further restoration of the eyelids was made, and free skin grafts, which were taken from the right upper lid, were placed in the defects created in the upper and lower lids of the left eye. The ectropion was corrected. At the third, and final, operation on Dec. 27, 1944, an artificial cavity was created to form a socket, and an epidermal graft was taken from the upper part of the left thigh and placed around a stent and inserted into the socket, with a resultant skin-lined socket which retained a prosthesis well.

DISCUSSION

DR WENDELL L. HUGHES, Hempstead, N. Y. Dr Fread is to be congratulated on the excellent result he has obtained in this case.

He rightly emphasizes the importance of surgical repair of the lid first, before attempting reconstruction of the socket

DR WILLIAM B DOHERTY Where was the cartilaginous graft obtained?

DR BERNARD FRAD From stock—from the cadaver

Ocular Manifestations of Dermatologic Diseases DR NATHAN SOBEL

Twenty-three ocular manifestations of dermatologic disease were presented. These diseases of the skin were discussed briefly and the more important aspects emphasized, as follows

Dermatitis venenata is the commonest disease of the eyelids. It is characterized by erythema, edema and, in the more severe forms, vesiculation and oozing. Scaling is often present. It is due to substances coming in contact with the eyelids in the following ways: (a) by direct application, e g, cosmetics, soaps and nickel or synthetic spectacle frames, (b) through the fingers, e g, nail polish, (c) by volatilization, e g, formaldehyde or perfumes. These substances are usually not primary irritants but produce the reaction as the result of allergic hypersensitivity. The dermatitis may also result from the local application of medicaments containing drugs which are allergenic, hence sensitizing, e g, sulfonamide compounds. The cause may be determined by means of patch tests and/or the elimination of the suspected substance. Industrial factors are easily determined, others, sometimes with great difficulty. The treatment consists of elimination of the irritant and mild local applications, such as wet dressings with boric acid or isotonic saline solution and boric acid ointment or petrolatum.

Basal cell carcinoma occasionally occurs on the eyelids. The clinical feature is the presence of pearly nodules peripherally, often with central ulceration. The diagnosis should be confirmed by biopsy. If the lesion is small, this examination may be made after removal of the tumor. This type of epithelioma is locally highly destructive but does not metastasize. The treatment, therefore, consists in complete removal by any of the following methods: excision, desiccation and curettage and/or radiotherapy.

Surgical Treatment of Primary Glaucoma. DR C S O'BRIEN, Iowa City

This paper will be published in full in a later issue of the ARCHIVES

DISCUSSION

DR JOHN H DUNNINGTON In this excellent discussion of the surgical treatment of primary glaucoma, Dr O'Brien has mentioned many important points, a few of which can be elaborated on. He rightly states that "treatment should be guided by the damage to function and not by the state of the intraocular pressure." Too great reliance on tonometric readings is a commonplace mistake, which can be avoided only by repeated perimetric studies. Knowledge of the status of the intraocular tension is essential, but it indicates only the probable trend of events. In my experience, the unreliability of this test has been greatest with patients of the older age group. While this

word of caution must be emphasized, I agree that early operation should be the rule rather than the exception

Dr O'Brien's choice of surgical procedures is in accord with generally accepted ideas. I agree that with the aid of retrobulbar anesthesia any operation for glaucoma may be performed with local anesthesia, but in cases of the acute primary type I prefer induction of general anesthesia with pentothal sodium. I am glad to subscribe to Dr O'Brien's indorsement of iridectomy ab externo in cases of acute narrow angle glaucoma. Both the keratome and the Graefe knife are dangerous instruments in the presence of a shallow anterior chamber, so if one can avoid introducing them into the anterior chamber so much the better. I have had no experience with his method of scleral fixation but can see no possible objection to its use. Cyclodialysis has not proved satisfactory in my hands except in cases of secondary glaucoma which follows cataract extraction. I have tried all variations in technic in an attempt to reduce the incidence of postoperative hemorrhage, without much success. In my hands it is not the simple operation which many authors proclaim it to be.

The technic advocated by Dr O'Brien in the Lagrange operation is a safe one, and I am sure that if this scratch method is routinely employed fewer complications will follow this operation. With such an external approach one has more accurate control of the amount of sclera to be resected.

Refinements in surgical technic are so important that I am grateful to Dr O'Brien for having focused attention on these practical details. Consciously or unconsciously, he has preached the doctrines of safety and simplicity—the two watchwords in ophthalmic surgery—and for this I wish to express my thanks. He has told us in a few words the value of certain procedures—simple to do and safe to use.

DR DANIEL B. KIRBY. I agree with Dr O'Brien's conclusions, and, inasmuch as I cannot improve on them, I shall merely supplement them with some of my own observations on other phases of surgical procedures for glaucoma.

First, with respect to the approach in treatment of glaucoma complicating cataract. If the tension can be held to normal with pilocarpine, the cataract may well be removed at the first operation, with or without iridectomy. If the tension cannot be held to normal with pilocarpine, a preliminary filtration is necessary. If the capsule of the lens is injured during operation for glaucoma, the situation becomes complicated. The extracapsular extraction is not so good as the intracapsular in the presence of glaucoma. The latter is indicated, also, because the zonule is fragile. The cataract should not be extracted until at least two months after filtration if the delay is feasible. If the tension after filtration is fairly low, the section for cataract extraction may well pass through the filtration area, in order to sclerose it somewhat and raise the tension. If the tension is normal, the incision should avoid the filtration area but should be made in the upper half of the limbus. Part of it may well be corneal. The functioning areas of the angle should not be interfered with any more than is necessary.

Good appositional sutures should be used in all cataract operations, particularly when glaucoma is a complication, and I can recommend

those which I use after the section has been made. The central traction suture is useful for lifting the corneal flap and avoiding injury to the endothelium. I should partly fill the anterior chamber with saline solution after the extraction and avoid the use of atropine in the postoperative course.

In the case of "glaucoma capsulare," namely, exfoliation of the lens capsule with glaucoma, extraction of the lens in its capsule is indicated at the first operation if this can be done without undue hemorrhage and without rapid decompression of the eye. This is possible if the tension is not over 30 mm. of mercury (Schiotz) and there is no congestion.

In the case of acute glaucoma which is not controlled with non-surgical measures, I have found preliminary posterior drainage a safeguard before the iridectomy or the iridencleisis, which is done immediately. Postscleral puncture with a knife has fallen into disrepute because of hemorrhage and other complications. I use local anesthesia and do a scleral trephination inferotemporally. This area is most easily approached and represents one of the areas of the usual field defects of glaucoma. After the trephine button has been removed, the choroid bulges. A barrage is made around the trephine hole by means of surface coagulation to prevent detachment of the retina. Perforating coagulation of the choroid and retina allows posterior decompression. The changes in the anterior part of the eye are usually gratifying and render easier the anterior filtering operation which is necessary, as the posterior drainage is only temporary in its effect.

Reoperation for glaucoma always presents a problem, and a more difficult one than does the first operation. Certainly if for example, a trephination has failed, it is hardly good judgment to repeat it. I should try something else. It is always hard to decide what would be better, but, on principle, if a procedure has not been successful, it will hardly have better results on the second trial. In order to demonstrate the efficiency of filtration and the presence or absence of sclerosed tissue after operation for glaucoma, I use a drop of tetracaine, and with a blunt probe I test for pitting and mobility of conjunctival and subconjunctival tissues.

Glaucoma presents complex problems, and, try as one will, one cannot always solve them. The patient must accept the responsibility for having such a complicated eye. One can only do one's best to get him out of his difficulty.

SIR W. STEWART DUKE-ELDER, London, England. I do not think it is wise of your chairman to ask me to speak before this Academy, for I have come to New York to learn ophthalmology, after having been four years at war, rather than to talk to you. I think the point to be stressed is what Dr. O'Brien describes aptly as his pessimism concerning the methods of treating primary glaucoma. When I was young, I used to be optimistic about glaucoma, but after years of seeing one's own patients come back, as well as the patients of other surgeons, I do not think any one who is honest can legitimately retain such optimism. In operation one is merely treating the end results of a symptom common to a number of diseases, the causes of which

are unknown. To treat diseases of the ankle, the knee and the hip all in the same way because they hinder locomotion would be analogous to some of the surgical attempts which are being made to control intraocular tension, and this crude therapy must continue until ophthalmologists come to know something of what they are trying to treat.

With everything that Dr. O'Brien has said I should agree, with one exception. He stated that in deciding on operation function, rather than tension, should be one's guide. That, of course, is true in more than 95 per cent of cases of glaucoma but there is one type which I think requires operation even if there is no increase in tension and no functional loss. That is the type I call neurovascular glaucoma occurring in a person who has acute but transient increases in tension which tend periodically to recur. I think in cases of this type that a small peripheral iridectomy or, even what does less trauma to the eye, a peripheral iridodialysis is a good prophylactic measure, even though the vision and fields are normal, particularly when the patient intends to leave a place where good and ready surgical treatment is available to go where adequate treatment is less accessible. That I think is an operation which is justified, otherwise, there is no question about the truth of the generalization that function is much more important than tension as a therapeutic guide.

Iridectomy ab externo I am glad to hear talked about. Like Dr. Dunnington, I think that on the whole I do fewer cyclodialyses and more iridencleises than Dr. O'Brien does. The important thing to be learned from the discussion, however, is that we ophthalmologists are all groping in darkness in our methods of therapeutics and must continue to do so until the etiologic factors in the various types of glaucoma are clarified.

DR. HAROLD F. WHALMAN, Los Angeles. The success of corneosclerectomy, as performed in the Elliott operation, the Lagrange operation or any of their modifications, depends on the most careful attention to detail in the obtaining of a properly functioning bleb. How may this be achieved?

I want first to call attention to a detail of technic performed by a distinguished countryman and colleague of Sir Stewart Duke-Elder, namely, Col. Robert E. Wright, who for thirty years was government ophthalmic surgeon at Madras, India, and who visited ophthalmologists in Los Angeles in 1936, just before the termination of that service.

Colonel Wright advised dissecting the conjunctiva separately to the limbus and then dissecting the episcleral tissue as a separate layer down to the limbus, where the cornea was split in the usual manner. Then, after the trephine opening was made, the episcleral tissue was carefully washed of blood clots to prevent heavy organization and laid loosely back over the opening. The conjunctiva was then united over the episcleral pad with a running suture. This loose episcleral pad, he felt, increased the formation of a bleb.

A detail which it has been my practice to observe is the use of physostigmine after operation to produce a gaping of the peripheral iridectomy wound and to prevent the iris from adhering to the trephine opening. As soon as the anterior chamber has reformed, which is

generally the next day, a mydriatic may be used to relieve any traumatic iritis

I agree with Dr O'Brien that it is important to start gentle massage the next day to facilitate formation of the bleb

If these precautions fail and a functioning bleb is not obtained it is not always necessary to perform a second complete trephination. One may nick the conjunctiva 4 or 5 mm to one side of the bleb and separate the adhesions over the trephine opening with an Elschnig cyclodialysis spatula. Or one may be able to make a new flap without the need of a second trephining.

If hypotony should occur, cauterization with trichloroacetic acid, heat or electrocoagulation will toughen the bleb. The thermophore may be applied at 145 C for one minute if desired.

I should say that goniotomy is a procedure which demands one's attention. Generally it is most satisfactory in cases of the deep chamber type of glaucoma in which there are no adhesions between the iris and the anterior annular line of Schwalbe. The only way this can be ascertained is by gonioscopic examination. I do not know how any ophthalmologist can intelligently treat glaucoma without study of the eye with this means. Furthermore, a shallow chamber may be converted into a deep one just before operation so that goniotomy may be employed if no or few adhesions are yet present.

Goniotomy, of course, has proved most successful with congenital glaucoma. On the West Coast, Dr Otto Barkan has been the outstanding proponent of this procedure for this condition. His results have been excellent, and his writings on the subject are worthy of the attention of every one.

DR C S O'BRIEN, Iowa City. I omitted one of the most important points in cyclodialysis. I believe that the reason for the disrepute into which this operation has fallen is that too little tissue is dialyzed. Several years ago one considered it sufficient if a third or less of the attachment of the ciliary body was dialyzed. Perhaps the reason I have more regard for the operation is that I dialyze only slightly less than one-half the area of attachment, staying away from the horizontal meridian. There is a large area of dialysis.

I was apparently misunderstood, for I am in complete agreement with Sir Stewart Duke-Elder and I often do a prophylactic iridectomy in an eye with a very shallow anterior chamber. It is a commendable procedure. My reason for doing it is that with a very shallow anterior chamber, an emotional upset, attendance at a movie or some other factor which causes the pupil to dilate may lead to blocking of the angle and the development of an acute narrow angle glaucoma whereas if an iridectomy has been done this is not possible. That happens with the neurovascular type of glaucoma.

Book Reviews

Das Gesichtsfeld (The Visual Field). By Hans Lauber, M D Price, 60 marks Pp 483, with 258 illustrations Munich J F Bergmann, Berlin and Vienna Springer-Verlag, 1944

While in Heidelberg last summer, I went to the medical book shops, with the hope of finding something new, interesting and unknown to the outside world. The stock was poor, and I found only Lauber's book. As I looked at the cover and read "Professor Hans Lauber, Kraków, 1944," I remembered that this was 1945 and that much had occurred in that part of Europe during the previous year. Where was Lauber now? And what of Kraków?

Lauber's book, which was printed in Vienna, is worth reading. Although the paper is rather thin, the illustrations are numerous and clear, and many are in color. In his introduction Lauber pays tribute to his predecessors, and particularly to Traquair. The first chapter is mainly historical, and the second describes the anatomic basis of field defects. An interesting physiologic study follows, which is concerned with normal limits, isopters, the visual field in dim light and at high altitudes and the normal color fields. Of some interest is his description of the attempt made by Harms, in 1940, to map an objective field using the pupillary response to light. The different isopters were traced by joining points corresponding to responses of one half, one third, one fifth, etc., of the standard macular response.

There is an excellent chapter which describes the various instruments in use. The importance of a neutral background is stressed. The surface of the perimeter arm should be dull, without visible landmarks, such as screws, on the side facing the patient. The perimeter arm should be 120 mm wide, and it should have a radius of not less than 330 mm. Fixation is best obtained by having the patient look at a small white ring, rather than at a small white spot. A small mirror could be used for fixation. Lauber believes that a spotlight is the best test object. There is a good description of the perimeters of McHardy, Maggiore, and Ferree and Rand.

Lauber has devised a perimeter which has a removable cloth surface. Lighting was studied carefully so that the Heidelberg colored papers would have the same value as in good daylight. He uses a 500 watt bulb with filters, so that the surface of the arc receives 200 lux. Lauber mentions stereoscopes and screens but seems to prefer the perimeter.

There is a lengthy description of the different charts used for recording the fields. The difficulty, similar to that in making geographic maps, is to obtain on a plane the most representative transcription of what occurs on a spherical surface. Lauber uses an equivalent polar projection. On his charts the field of the left eye is on the left side, so that the field is mapped as though one were in the patient's place, and not facing him.

All this first, and theoretic, part of the book is thorough and, on the whole, good. The second half of the book deals with field defects resulting from lesions in the eyes and in the optic pathways. Some chapters are better than others, but all are worth reading because they give Lauber's views on much outside perimetry. Multiple sclerosis is stressed as the most frequent cause of retrobulbar neuritis. Toxic amblyopia is considered to be due to alcohol more often than to tobacco.

This is in accord with views prevalent in Continental Europe and contrary to the teaching in the United States or in Great Britain. Only two pages are devoted to the visual disturbances resulting from sinus infection. There are good chapters on tabes and glaucoma, but the one dealing with chiasmal lesions is weak, probably because Lauber seems to have lacked personal experience with clinical material. This, in turn, is probably due to the backward state of neurosurgery in Germany as compared with its development in the United States, Great Britain and France. Lauber's description is too theoretic, as it is based on anatomy, whereas a clinical approach would have been better.

In the next chapter there is a good description of retrochiasmal field defects. There is an interesting discussion on sparing of the macula, for which Lauber, unfortunately, was not able to include any reference to Verhoeff's last paper (*A New Answer to the Question of Macular Sparing*, *ARCH OPHTH* 30:421 [Oct.] 1943).

Lauber believes that amblyopia ex anopsia is a clinical entity but that a careful study of the fundus will show organic lesions more frequently than is suspected at present. There is a good chapter on hysteria and on malingering, with several ingenious suggestions. The last chapter is concerned with the functional loss due to the various field defects and equitable compensation for the field loss.

There are numerous references after each chapter, without any apparent discrimination on a national or racial basis. American, British and French authors seem to be mentioned impartially, as are Jewish ones, whether of German or foreign origin. The fact that I noticed this may be a sad commentary on the times.

Lauber's book is the third volume of a series entitled "Ophthalmology of Today." I was unable to find the first two, which are "Introduction to Physiological Optics," by Arnim von Tschermack-Seysenegg, and "The Eye and Internal Secretions," by Carl Velhagen.

EDWARD HARTMANN

News and Notes

EDITED BY DR W. L. BENEDICT

GENERAL NEWS

American Orthoptic Council: Examinations for Technicians—The next examination by the American Orthoptic Council will be held in September and October 1946.

The written examinations will be held at various cities in the country on Friday, September 6. Only those passing the written examinations will be permitted to take the oral and practical tests, to be given in Chicago, Saturday, October 12.

Applications on official forms must be received before July 1, 1946.

Address the American Orthoptic Council, 23 East Seventy-ninth Street, New York 21.

SOCIETY NEWS

Association for Research in Ophthalmology—The fifteenth scientific meeting of the Association for Research in Ophthalmology will be held in the Mark Hopkins Hotel, San Francisco, Tuesday, July 2, 1946.

Directory of Ophthalmologic Societies *

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 Secretary Dr Arturo Etchemendigaray, Villa Constitución, Santa Fé
 Place Rosario Time Last Saturday of every month, April to November All correspondence should be addressed to the President

SOCIEDADE DE OFTALMOLOGIA DEL NORTE

President Dr Alberto Cardenas
 Secretary Dr Jorge Luis Castillo, Mendoza 421, Tucuman, Argentina

SOCIEDADE DE OFTALMOLOGIA DE MINAS GERAIS

President Prof Hilton Rocha, Rua Rio de Janeiro 2251, Bello Horizonte, Minas Geraes, Brazil
 Secretary Dr Ennio Coscarelli, Rua Aimorés 1697, Bello Horizonte, Minas Geraes, Brazil

SOCIEDADE DE OFTALMOLOGIA E OTORRINOLARINGOLOGIA DE RIO GRANDE DO SUL

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 Secretary Dr Fernando Voges Alves, Caixa Postal 928, Porto Alegre, Rio Grande do Sul

SOCIEDADE DE OPHTHALMOLOGIA E OTO-RHINO-LARYNGOLOGIA DA BAHIA

President Dr Theonilo Amorim, Barra Avenida, Bahia, Brazil

Secretary Dr Adroaldo de Alencar, Brazil

All correspondence should be addressed to the President

SOCIETA OPTALMOLOGICA ITALIANA

President Prof Dott Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome

Secretary Prof Dott Epimaco Leonardi, Via del Gianicolo, 1, Rome

SOCIÉTÉ FRANÇAISE D'OPHTALMOLOGIE

Secretary Dr René Onfray, 6 Avenue de la Motte Picquet, Paris, 7^e

SOCIETY OF SWEDISH OPHTHALMOLOGISTS

President. Prof K G Ploman, Stockholm

Secretary Dr K O Granstrom, Sodermalmsstorg 4, III tr, Stockholm, So

TEL AVIV OPHTHALMOLOGICAL SOCIETY

President Dr D Arieh-Friedman, 96 Allenby St, Tel Aviv, Palestine

Secretary Dr Sadger Max, 9 Bialik St, Tel Aviv, Palestine

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION
ON OPHTHALMOLOGY

Chairman Dr Frederick C Cordes, 384 Post St, San Francisco

Secretary Dr R J Masters, 23 E Ohio St, Indianapolis

Place San Francisco Time July 1-5, 1946

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY,
SECTION ON OPHTHALMOLOGY

President Dr Gordon B New, Mayo Clinic, Rochester, Minn

President-Elect Dr Alan C Woods, Johns Hopkins Hospital, Baltimore 5

Executive Secretary-Treasurer Dr William L Benedict, 100-1st Ave Bldg,
Rochester, Minn

Place Palmer House, Chicago Time Oct 13-18, 1946

AMERICAN OPHTHALMOLOGICAL SOCIETY

President Dr Eugene M Blake, 303 Whitney Ave, New Haven, Conn

Secretary-Treasurer Dr Walter S Atkinson, 129 Clinton St, Watertown, N Y

Place San Francisco Time June 26-28, 1946

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC

Chairman Dr Conrad Berens, 35 E 70th St, New York

Secretary-Treasurer Major Brittain F Payne, School of Aviation Medicine,
Randolph Field, Texas

Assistant Secretary-Treasurer Dr Hunter Romaine, 35 E 70th St, New York

CANADIAN MEDICAL ASSOCIATION, SECTION ON OPHTHALMOLOGY

President Dr Alexander E MacDonald, 170 St George St, Toronto 5

Secretary-Treasurer Dr L J Sebert, 170 St George St, Toronto 5

CANADIAN OPHTHALMOLOGICAL SOCIETY

President Walter W Wright, 170 St George St, Toronto 5

Secretary-Treasurer Dr Kenneth B Johnston, Suite 1, 1509 Sherbrooke St W,
Montreal

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS

President Mr Mason H Bigelow, 1790 Broadway, New York
 Secretary Miss Regina E Schneider, 1790 Broadway, New York
 Executive Director Mrs Eleanor Brown Merrill, 1790 Broadway, New York
 Place New York Time Nov 25-27, 1946

SECTIONAL

ACADEMY OF MEDICINE OF NORTHERN NEW JERSEY, SECTION ON
 EYE, EAR, NOSE AND THROAT

President Dr Anthony Ambrose, 71 Congress St, Newark
 Secretary Dr William F Keim Jr, 15 Washington St, Newark 2
 Place 91 Lincoln Park South, Newark Time 8 45 p m, second Monday of
 each month, October to May

CENTRAL ILLINOIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Stuart Broadwell, 101½ N 5th St, Springfield, Ill
 Secretary-Treasurer Dr William F Hubble, 861-867 Citizens Bldg, Decatur, Ill

CENTRAL WISCONSIN SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr P G Spelbring, 131 S Barstow St, Eau Claire
 Secretary Dr G L McCormick, 650 S Central Ave, Marshfield
 Place Gateway Hotel, Land O'Lakes Time May 18-19, 1946

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President Dr Howard F Hill, 177 Main St, Waterville, Maine
 Secretary-Treasurer Dr Merrill J King, 264 Beacon St, Boston 16
 Place Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston Time
 8 p m, third Tuesday of each month from November to April, inclusive

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President Dr D H O'Rourke, 1612 Tremont Pl, Denver
 Secretary-Treasurer Dr C Allen Dickey, 450 Sutter St, San Francisco

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr James H Mathews, 1317 Marion St, Seattle, Wash
 Secretary-Treasurer Dr Barton E Peden, 301 Stimson Bldg, Seattle 1
 Place Seattle or Tacoma, Wash Time Third Tuesday of each month except
 June, July and August

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President Dr J Sheldon Clark, Sterling, Ill
 Secretary-Treasurer Dr Harry R Warner, 321 W State St, Rockford, Ill
 Place Rockford, Ill, or Janesville or Beloit, Wis Time Third Tuesday of each
 month from October to April, inclusive

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr A R McKinney, 330 S Washington St, Saginaw, Mich
 Secretary-Treasurer Dr Harold H Heuser, 207 Davidson Bldg, Bay City, Mich
 Place Saginaw or Bay City, Mich Time Second Tuesday of each month, except
 July, August and September

SIoux VALLEY EYE AND EAR ACADEMY

President Dr J C Decker, 515 Francis Bldg, Sioux City, Iowa
 Secretary-Treasurer Dr J E Dvorak, 408 Davidson Bldg, Sioux City, Iowa

SOUTHERN MEDICAL ASSOCIATION, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman Dr John H Bursleson, 414 Navarro St, San Antonio, Texas

Secretary Dr J W Jervey Jr, 101 Church St, Greenville, S C

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President Dr H L Brehmer, 221 W Central Ave, Albuquerque, N Mex

Secretary Dr A E Cruthrds, 1011 Professional Bldg, Phoenix, Ariz

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President Dr W M Dodge, 716 First National Bank Bldg, Battle Creek

Secretary-Treasurer Dr Kenneth Lowe, 25 W Michigan Ave, Battle Creek

Time Last Thursday of September, October, November, March, April and May

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Ray Parker, 218 Franklin St, Johnstown, Pa

Secretary-Treasurer Dr J McClure Tyson, Deposit National Bank Bldg, Dubois

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President Dr E C Moulton, 619 Garrison Ave, Fort Smith

Secretary Dr K W Cosgrove, 7 Urquhart Bldg, Little Rock

COLORADO OPHTHALMOLOGICAL SOCIETY

President Dr George H Stine, 23 E Pikes Peak Ave, Colorado Springs

Secretary Dr J Leonard Swigert, 320 Republic Bldg, Denver

Place University Club, Denver Time 7 30 p m, third Saturday of each month.

October to May, inclusive

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON EYE, EAR,
NOSE AND THROAT

President Dr Paul B MacCready, 442 Temple St, New Haven

Secretary-Treasurer Dr W H Turnley, 1 Atlantic St, Stamford, Conn

EYE, EAR, NOSE AND THROAT CLUB OF GEORGIA

President Dr William O Martin Jr, Doctors Bldg, Atlanta

Secretary-Treasurer Dr C K McLaughlin, 666 Cherry St, Macon

INDIANA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr W E Stewart, 721 Wabash Ave, Terre Haute

Secretary Dr Russell A Sage, 23 E Ohio St, Indianapolis

Place French Lick Time First Wednesday in April

IOWA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr S A O'Brien, 1 N Federal Ave, Mason City

KANSAS STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY AND
OTOLARYNGOLOGY

President Dr W B Granger, Emporia

Secretary Dr George F Gsell, 911 Beacon Bldg, Wichita 2

LOUISIANA-MISSISSIPPI OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr George S Adkins, 121 N President St, Jackson, Miss

Secretary-Treasurer Dr Edley H Jones, 1301 Washington St, Vicksburg, Miss

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, SECTION ON
EYE, EAR, NOSE AND THROAT DISEASES

Chairman Dr William T Hunt Jr, 1205 Spruce St, Philadelphia 7
Secretary Dr Gabriel Tucker, 250 S 18th St, Philadelphia 3

MICHIGAN STATE MEDICAL SOCIETY, SECTION OF OPHTHALMOLOGY
AND OTOLARYNGOLOGY

Chairman Dr Edmond L Cooper, 1553 Woodward Ave, Detroit 26
Secretary Dr Ralph H Gilbert, 110 Fulton St E, Grand Rapids

MINNESOTA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Karl C Wold, 1051 Lowry Bldg, St Paul 2
Secretary Dr William A Kennedy, 372 St Peter St, St Paul 2
Time Second Friday of each month from October to May

MONTANA ACADEMY OF OTO-OPHTHALMOLOGY

President Dr H Casebeer, 44 W Park Ave, Butte
Secretary Dr Fritz D Hurd, 309 Medical Arts Bldg, Great Falls

NEBRASKA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha
Secretary-Treasurer Dr John Peterson, 1307 N St, Lincoln

NEW JERSEY STATE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY,
OTOLOGY AND RHINOLARYNGOLOGY

Chairman Dr George P Meyer, 410 Haddon Ave, Camden
Secretary Dr John P Brennan, 429 Cooper St, Camden

NEW YORK STATE MEDICAL SOCIETY, EYE, EAR, NOSE
AND THROAT SECTION

Chairman Dr Maxwell D Ryan, 660 Madison Ave, New York 21
Secretary Dr Thomas H Johnson, 30 W 59th St, New York

NORTH CAROLINA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr A J Ellington, 412 S Spring St, Burlington
Secretary Dr J A Harrill, Bowman Gray School of Medicine, Winston-Salem
Place Hendersonville Time Sept 16-19, 1946

NORTH DAKOTA ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr W L Diven, City National Bank Bldg, Bismarck
Secretary-Treasurer Dr A E Spear, 20 W Villard, Dickinson

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Wilfred Belnap, 833 S W 11th Ave, Portland
Secretary-Treasurer Dr C W Kuhn, 1020 S W Taylor St, Portland 5
Place Good Samaritan Hospital, Portland Time Third Tuesday of each month.

PENNSYLVANIA ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Thomas F Furlong Jr, 36 Parking Plaza, Ardmore
Secretary Dr Benjamin F Souders, 143 N 6th St, Reading
Time Last week in April

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President Dr N Darrell Harvey, 112 Waterman St, Providence
 Secretary-Treasurer Dr Linley C Happ, 124 Waterman St, Providence
 Place Rhode Island Medical Society, Library, Providence Time 8 30 p m,
 second Thursday in October, December, February and April

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr J H Stokes, 125 W Cheves St, Florence
 Secretary-Treasurer Dr Roderick Macdonald, 330 E Main St, Rock Hill
 Place Hendersonville, N C Time Sept 16-19, 1946

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr George Burchfield, Maryville
 Secretary-Treasurer Dr Sam H Sanders, 1089 Madison Ave, Memphis

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President Dr F H Rosebrough, 603 Navarro St, San Antonio
 Secretary Dr M K McCullough, 1717 Pacific Ave, Dallas

UTAH OPHTHALMOLOGICAL SOCIETY

President Dr E B Fairbanks, 315 Medical Arts Bldg, Salt Lake City
 Secretary-Treasurer Dr Dean Spear, 516 Boston Bldg, Salt Lake City
 Place University Club, Salt Lake City Time 7 00 p m, third Monday of
 each month

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President Dr Thomas E Hughes, 1000 W Grace St, Richmond
 Secretary-Treasurer Dr Francis H McGovern, 105 S Union St, Danville

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND
THROAT SECTION

President Dr George Traugh, 309 Cleveland Ave, Fairmont
 Secretary Dr Welch England, 621½ Market St, Parkersburg

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr E L Mather, 39 S Main St, Akron, Ohio
 Secretary-Treasurer Dr V C Malloy, 2d National Bank Bldg, Akron, Ohio
 Time First Monday in January, March, May and November

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President Dr B M Cline, 153 Peachtree St N E, Atlanta, Ga
 Secretary Dr Lester A Brown, 815 Doctors Bldg, Atlanta, Ga
 Place Academy of Medicine Time 7 30 p m, fourth Monday of each month
 from October to May

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman Dr Jonas Friedenwald, 1212 Eutaw Pl, Baltimore
 Secretary Dr Fred Reese, 330 N Charles St, Baltimore 1
 Place Medical and Chirurgical Faculty, 1211 Cathedral St Time 8 30 p m,
 fourth Thursday of each month from October to March

BIRMINGHAM EYE, EAR, NOSE AND THROAT CLUB

President Each member, in alphabetical order
 Secretary Dr W Chunn Parsons, 425 Woodward Bldg, Birmingham, Ala
 Place Tutwiler Hotel Time 6 30 p m, second Tuesday of each month, September to May, inclusive

BROOKLYN OPHTHALMOLOGICAL SOCIETY

President Dr Michael J Buonaguro, 589 Lorimer St, Brooklyn 11
 Secretary-Treasurer Dr Louis Freimark, 256 Rochester Ave, Brooklyn 13
 Place Kings County Medical Society Bldg, 1313 Bedford Ave Time Third Thursday in February, April, May, October and December

BUFFALO OPHTHALMOLOGIC CLUB

President Dr William H Howard, 389 Linwood Ave, Buffalo 9
 Secretary-Treasurer Dr Sheldon B Freeman, 196 Linwood Ave, Buffalo 9
 Time Second Thursday of each month from October to May

CHATTANOOGA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Each member, in alphabetical order
 Secretary Dr. Douglas Chamberlain, Chattanooga Bank Bldg, Chattanooga, Tenn
 Place Mountain City Club Time Second Thursday of each month from September to May

CHICAGO OPHTHALMOLOGICAL SOCIETY

President Dr W A Mann, 30 N Michigan Ave, Chicago 2
 Secretary Dr J R Fitzgerald, 3215 W North Ave, Chicago
 Place Continental Hotel, 505 N Michigan Ave Time Third Monday of each month from October to May

CINCINNATI GENERAL HOSPITAL OPHTHALMOLOGY STAFF

Chairman Dr D T Vail, 441 Vine St, Cincinnati
 Secretary Dr A A Levin, 441 Vine St, Cincinnati
 Place Cincinnati General Hospital Time 7 45 p m, third Friday of each month except June, July and August

CLEVELAND OPHTHALMOLOGICAL CLUB

Chairman Dr M Paul Motto, Rose Bldg, Cleveland
 Secretary Dr H H Wygand, 624 Guardian Bldg, Cleveland
 Time Second Tuesday in October, December, February and April

COLLEGE OF PHYSICIANS, PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Chairman Dr Burton Chance, 317 S 15th St, Philadelphia
 Clerk Dr George F J Kelly, 37 S 20th St, Philadelphia
 Time Third Thursday of every month from October to April, inclusive

COLUMBUS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

Chairman Dr M Goldberg, 328 E State St, Columbus, Ohio
 Secretary-Treasurer Dr W J Miller, 21 E State St, Columbus, Ohio
 Place University Club Time 6 15 p m, first Monday of each month, from October to May, inclusive

CORPUS CHRISTI EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Dr L W O Janssen, 710 Medical Professional Bldg, Corpus Christi, Texas
 Secretary Dr F B Kelly, 519 Medical Professional Bldg, Corpus Christi, Texas
 Time 6 30 p m, third Tuesday of each month from October to May

DALLAS ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Ruby K. Daniel, Medical Arts Bldg, Dallas 1, Texas

Secretary Dr Tom Barr, Medical Arts Bldg, Dallas 1, Texas

Place Dallas Athletic Club Time 6 30 p m, first Tuesday of each month from October to June The November, January and March meetings are devoted to clinical work.

DES MOINES ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr H I McPherrin, 406-6th Ave, Des Moines, Iowa

Secretary-Treasurer Dr C C Jones, Bankers Trust Bldg, Des Moines, Iowa

Time 7 45 p m, fourth Monday of every month from September to May

DETROIT OPHTHALMOLOGICAL CLUB

Chairman Members rotate alphabetically

Secretary Dr Wesley G Reid, 974 Fisher Bldg, Detroit 2

Place Club rooms of Wayne County Medical Society Time First Monday of each month, November to April, inclusive

DETROIT OPHTHALMOLOGICAL SOCIETY

President Dr Bruce Fralick,

Secretary Dr William S Gonne, 619 David Whitney Bldg, Detroit 26

Place Club rooms of Wayne County Medical Society Time 6 30 p m, third Thursday of each month from November to April, inclusive

EASTERN NEW YORK EYE, EAR, NOSE AND THROAT ASSOCIATION

President Dr Frank C Furlong, 713 Union St, Schenectady

Secretary-Treasurer Dr E Martin Freund, 762 Madison Ave, Albany

Time Third Wednesday in October, November, March, April, May and June

FORT WORTH EYE, EAR, NOSE AND THROAT SOCIETY

President Dr C R Lees, 602 W 10th St Fort Worth 2, Texas

Secretary-Treasurer Dr Van D Rathgeber, 1305 Medical Arts Bldg, Fort Worth, Texas

Place Medical Hall, Medical Arts Bldg Time 7 30 p m, first Friday of each month except July and August

HOUSTON ACADEMY OF MEDICINE, OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SECTION

President Dr J Matt Robison, 1304 Walker Ave, Houston, Texas

Secretary Dr John H Barrett, 1304 Walker Ave, Houston, Texas

Place Medical Arts Bldg, Harris County Medical Society Rooms Time 8 p m, second Thursday of each month from September to June

INDIANAPOLIS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr J Jerome Littell, 603 Hume Mansur Bldg, Indianapolis

Secretary Dr J Lawrence Sims, 303 Hume Mansur Bldg, Indianapolis

Place Indianapolis Athletic Club Time 6 30 p m, second Thursday of each month from November to May

KANSAS CITY SOCIETY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Edgar Johnson, 906 Grand Ave, Kansas City, Mo

Secretary Dr W E Keith, 1103 Grand Ave, Kansas City, Mo

Time Third Thursday of each month from October to June The November, January and March meetings are devoted to clinical work

LONG BEACH EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Dr Francis Carl Hertzog, 117 E 8th St, Long Beach, Calif
 Secretary-Treasurer Dr Robert G Thornburgh, 117 E 8th St, Long Beach, Calif
 Place Seaside Hospital Time Last Wednesday of each month from October to May

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr A R Robbins, 930 Wilshire Blvd, Los Angeles
 Secretary-Treasurer Dr K C Brandenburg, 110 Pine Ave, Long Beach 2, Calif
 Place Los Angeles County Medical Association Bldg, 1925 Wilshire Blvd Time
 6 30 p m, fourth Monday of each month from September to May, inclusive

LOUISVILLE EYE AND EAR SOCIETY

President Dr Joseph S Heitger, Heyburn Bldg, Louisville, Ky
 Secretary-Treasurer Dr J W Fish, 321 W Broadway, Louisville, Ky
 Place Brown Hotel Time 6 30 p m, second Thursday of each month from September to May, inclusive

LOWER ANTHRACITE EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Each member in alphabetical order
 Secretary Dr James J Monohan, 31 S Jardin St, Shenandoah, Pa

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION OF
 OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Dr P S Constantinople, 1835 I St N W, Washington
 Secretary Dr Frazier Williams, 1801 I St N W, Washington
 Place 1718 M St N W Time 8 p m, third Friday of each month from October to April, inclusive

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Each member, in alphabetical order
 Secretary Dr Sam H Sanders, 1089 Madison Ave, Memphis, Tenn
 Place Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital Time 8 p m,
 second Tuesday of each month from September to May

MILWAUKEE OTO-OPHTHALMIC SOCIETY

President Dr Ralph T Rank, 238 W Wisconsin Ave, Milwaukee
 Secretary-Treasurer Dr Frank G Treskow, 411 E. Mason St, Milwaukee 2
 Place University Club Time 6 30 p m, fourth Tuesday of each month from October to May

MONTGOMERY COUNTY MEDICAL SOCIETY

Chairman Dr H V Dutrow, 1040 Fidelity Medical Bldg, Dayton, Ohio
 Secretary-Treasurer Dr Maitland D Place, 981 Reibold Bldg, Dayton, Ohio
 Place Van Cleve Hotel Time 6 30 p m, first Tuesday of each month from October to June, inclusive

MONTREAL OPHTHALMOLOGICAL SOCIETY

President Dr J Rosenbaum, 1396 Ste Catherine St W, Montreal, Canada
 Secretary Dr L Tessier, 1230 St Joseph Blvd E, Montreal, Canada.
 Time Second Thursday of October, December, February and April

NASHVILLE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

Chairman Dr M M Cullom, 700 Church St, Nashville, Tenn
 Secretary Dr R E Sullivan, 432 Doctors Bldg, Nashville 3, Tenn
 Place James Robertson Hotel Time 6 30 p m, third Monday of each month from October to May

NEW ORLEANS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

President Dr W B Clark, 1012 American Bank Bldg, New Orleans
 Secretary Dr Mercer G Lynch, 1018 Maison Blanche Bldg, New Orleans
 Place Louisiana State University Medical Bldg Time 8 p m, second Tuesday
 of each month from October to May

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman Dr Brittain F' Payne, 17 E 72d St, New York 21
 Secretary Dr Milton Berliner, 57 W 57th St, New York
 Time 8 30 p m, third Monday of every month from October to May, inclusive

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President Dr Benjamin Friedman, 6 W 77th St, New York
 Secretary Dr Benjamin Esterman, 983 Park Ave, New York 28
 Place New York Academy of Medicine, 2 E 103d St Time 8 p m, first Monday
 of each month from October to May, inclusive

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President Dr Harvey O Randel, 117 N Broadway, Oklahoma City
 Secretary Dr S R Shaver, 117 N Broadway, Oklahoma City
 Place University Hospital Time Second Tuesday of each month from Sep-
 tember to May

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND
OTO-LARYNGOLOGICAL SOCIETY

President Dr A A Steinberg, 1502 Farnam St, Omaha
 Secretary-Treasurer Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha 2
 Place Omaha Club, 20th and Douglas Sts, Omaha Time 6 p m dinner, 7 p m
 program, third Wednesday of each month from October to May

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President Dr Thomas Sanfacon, 340 Park Ave, Paterson, N J
 Secretary-Treasurer Dr J Averbach, 435 Clinton Ave, Clinton, N J
 Place Paterson Eye and Ear Infirmary Time 9 p m, last Friday of every
 month, except June, July and August

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

President Dr Isaac Tassman, 136 S 16th St, Philadelphia
 Secretary Dr Glen Gregory Gibson, 255 S 17th St, Philadelphia
 Time First Thursday of each month from October to May

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

President Dr Clarence F Bernatz, Park Bldg, Pittsburgh
 Secretary Dr Robert J Billings, Park Bldg, Pittsburgh
 Place Pittsburgh Academy of Medicine Bldg Time Fourth Monday of each
 month, except June, July, August and September

READING EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Claude W Bankes, 212 N 6th St, Reading, Pa
 Secretary Dr Paul C Craig, 232 N 5th St, Reading, Pa
 Place Wyomissing Club Time 6 30 p m, third Wednesday of each month from
 September to July

RICHMOND EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Luther C Brawner, Professional Bldg, Richmond, Va
 Secretary Dr Clifford A Folkes, Professional Bldg, Richmond, Va
 Place Westmoreland Club Time 6 p m, second Monday of each month from
 October to May

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President Dr Frank Barber, 75 S Fitzhugh St, Rochester, N Y
 Secretary-Treasurer Dr Charles T Sullivan, 277 Alexander St, Rochester, N Y

ST LOUIS OPHTHALMIC SOCIETY

President Dr Vincent Jones, 634 N Grand Blvd, St Louis
 Secretary Dr T E Sanders, 508 N Grand Blvd, St Louis 3
 Place Oscar Johnson Institute Time Fourth Friday of each month from October
 to April, inclusive, except December, at 8 00 p m

SAN ANTONIO OPHTHALMO-OTO-LARYNGOLOGICAL SOCIETY

President Dr Belvin Pritchett, 705 E Houston St, San Antonio 5, Texas
 Secretary-Treasurer Lt Col John L Matthews, AAF School of Aviation Medicine,
 Randolph Field, Texas
 Place San Antonio, Brooke General Hospital, Randolph Field or San Antonio
 Aviation Cadet Center Time 7 p m, second Tuesday of each month from
 October to May

SAN FRANCISCO COUNTY MEDICAL SOCIETY, SECTION ON EYE,
 EAR, NOSE AND THROAT

Chairman Dr C B Cowan, 490 Post St, San Francisco
 Secretary Dr D Harrington, 384 Post St, San Francisco
 Place Society's Bldg, 2180 Washington St, San Francisco Time Fourth
 Tuesday of every month except June, July and December

SHREVEPORT EYE, EAR, NOSE AND THROAT SOCIETY

President Dr David C Swearingen, Slattey Bldg, Shreveport, La
 Secretary-Treasurer Dr Kenneth Jones, Medical Arts Bldg, Shreveport, La
 Place Shreveport Charity Hospital Time 7 30 p m, first Monday of every
 month except July, August and September

SPOKANE ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President Dr Clarence A Veasey Sr, 421 W Riverside Ave, Spokane, Wash
 Secretary Dr Clarence A Veasey, 421 W Riverside Ave, Spokane, Wash
 Place Spokane Medical Library Time 8 p m, fourth Tuesday of each month
 except June, July and August

SYRACUSE EYE, EAR, NOSE AND THROAT SOCIETY

President Dr A H Rubenstein, 713 E Genesee St, Syracuse, N Y
 Secretary-Treasurer Dr I H Blaisdell, 713 E Genesee St, Syracuse, N Y
 Place University Club Time First Tuesday of each month except June, July
 and August

TOLEDO EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Dr W W Randolph, 1838 Parkwood Ave, Toledo 2, Ohio
 Secretary Dr John L Roberts, 316 Michigan St, Toledo, Ohio
 Place Toledo Club Time Each month except June, July and August

TORONTO ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman Dr R G C Kelly, 14 Lynwood Ave, Toronto 5, Canada

Secretary Dr Alfred Elliott, 802 Medical Arts Bldg, Toronto 5, Canada

Place Academy of Medicine, 13 Queens Park Time First Monday of each month, November to April

WASHINGTON, D C, OPHTHALMOLOGICAL SOCIETY

President Dr Harold M Downey, 1740 M St N W, Washington, D C

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COLOR VISION AND RECENT DEVELOPMENTS IN COLOR VISION TESTING

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THIS report is a brief, greatly simplified expression of the working hypotheses being used by color vision investigators today, a note on the ICI Coordinate System and Standard Observer, a short report on some of the developments resulting from Inter-Society Color Council (ISCC) and other activities, a notation of some typical color vision tests in current use, and an empiric classification of the types of color vision we have found in our studies.

The first two sections are simplified abstracts arranged, we hope, in a form easy to remember. The third section is really a news note and the fourth section hardly more than a short list of typical examples of color vision tests. For the fifth section we claim neither originality nor completeness. It is a practical, easily remembered outline into which we have been able satisfactorily to fit all the types of color vision so far encountered by us. We have not yet met what we thought was tetartanopia. Such a defect would probably require an addition to our classification.

I. A WORKING HYPOTHESIS FOR STUDYING COLOR VISION

There are

THREE FACTORS IN COLOR SEEING

1. *The illuminant (ICI-C)*
2. *The eye (Standard Observer)*
3. *The object (test material)*

Confusion in color testing results from lack of standardization and specification of conditions of the test. To test one factor the other two must be held constant. No test for color vision is reliable unless the characteristics of both the illuminant and the test material are known.

From the Knapp Memorial Laboratories, Institute of Ophthalmology, Columbia University College of Physicians and Surgeons

The illuminant is a tool used to perform a task, and good or poor performance will result from using an efficient or an ineffective tool

The *illuminant* which should be used for all daylight color vision testing is International Commission on Illumination (I C I) Illuminant C, or its nearest practical equivalent. This illuminant is representative of overcast skylight, which has an average color temperature of about 6,700°K

The same commission has adopted as a standard eye for providing specifications of test materials the so-called *Standard Observer* (a hypothetical observer whose color responses conform to those of the mean, statistically computed of observers having normal color vision)

Standard test materials have not yet been adopted

There are

THREE STANDARD ICI ILLUMINANTS

- 1 ICI-A
- 2 ICI-B
- 3 ICI-C

The International Commission on Illumination (ICI) in 1931 adopted as international standards three illuminants, known as ICI Illuminant A, ICI Illuminant B and ICI Illuminant C. Illuminant A represents the illumination provided by a gas-filled tungsten lamp operating at a color temperature of 2,848°K (roughly a 75 watt lamp operating at rated voltage). Illuminant B approximates a color temperature of 4,800°K, which corresponds roughly to noon sunlight. Illuminant C approximates a color temperature of 6,700°K and represents average overcast skylight (average daylight).

While good color vision tests may be devised for any illuminant, most of the commonly used tests have been designed for daylight illumination and are not effective under other illuminants. Hence, ICI Illuminant C is the standard for use in daylight color testing work. The actual ICI standard being specified as a liquid filter to be used with ICI Illuminant A is inconvenient to prepare and use. The only near and practical equivalent is a Macbeth daylight lamp (tungsten lamp plus filter of Corning Daylight glass), designed to operate at approximately 6,700°K.

There are

THREE FACTORS IN THE ILLUMINANT

- 1 *Quality, or spectral composition*—daylight values
- 2 *Distribution*—even, illuminate at 45 degree angle, view at 90 degree angle
- 3 *Quantity, or amount*—10 to 60 foot candles

There are three factors to be considered in the light or illuminant used to view the color test materials

1 The quality, or spectral composition, of the light is of extreme importance. Obviously, green material cannot be correctly seen under a red light or vice versa. Most color testing is strongly influenced, and usually invalidated, by improper or haphazard choice of the illuminant. "Daylight," in the sense that it means whatever comes through the window, has but little value as a specification. For precise testing the spectral distribution of the illuminant should approximate as closely as possible that of ICI Illuminant C.

In scientific work, the one filter generally used to provide the nearest equivalent to this is Corning filter 590. This is available commercially in daylight lamps made by the Macbeth Daylighting Company.

2 The lighting should provide uniform distribution and, in order to avoid reflected glare, should fall on the test material at an angle of approximately 45 degrees, in which case the angle of view of the observer should be normal, or 90 degrees.

3 Extensive testing has shown that with other factors held constant a change in density of incident luminous flux causes no significant change between 10 and 60 foot candles. Since there is usually some stray light in the room, it is preferable to keep the general room illumination low and to use 50 to 60 foot candles from ICI Illuminant C on the test material—the higher level thus preventing interference with reliable results by small amounts of extraneous illumination from nonstandard sources, reflection from colored walls, etc.

There are

THREE FACTORS IN THE COLOR VISION MECHANISM.

- 1 *Proto, or first* (Helmholtz's red component)
- 2 *Deutero, or second* (Helmholtz's green component)
- 3 *Trito, or third* (Helmholtz's violet or blue component)

On the basis of the physical law of color mixing that all normal color sensations can be obtained by integrating the proper proportions of three primaries, i. e., red, green and violet or blue (additive mixtures) or by filtering from the illuminant the proper proportions of these three primaries (subtractive mixtures), it is assumed that there are three physiologic processes, each of which responds dominantly to its adequate stimulus or wavelength and all of which respond in certain proportions to all wavelengths—the integrated responses thus comprising one's color experiences.

This classification (*proto-deutero-trito*) follows naturally from the widely used terminology suggested by von Kries as a factual, non-theoretic description of the three classes of dichromasy (see page 607).

Although there are theories today which seem to satisfy all the facts of color vision (G. E. Muller, E. Q. Adams), the two best known theories are still those of Helmholtz (based on three components a

red component, a green component and a violet or blue component) and of Hering (based on three reversible pairs of processes red-green, yellow-blue and black-white) The Helmholtz theory is useful for classifying types of color confusions, the Hering theory is convenient in explaining color perceptions and such phenomena as after-images and peripheral field limits Neither theory accounts for all the facts of normal and abnormal color vision, but with the use of each where it fits best and of the von Kries terminology to avoid reference to a single color theory one has a basis for classification that provides for

THREE TYPES OF COLOR VISION

- 1 *Trichromatic*
- 2 *Dichromatic*
- 3 *Monochromatic*

Trichromatic color vision is the normal result of unimpeded response by all three physiologic processes in their normal proportions, dichromatic color vision occurs when there are only two differentiated processes, and monochromatic vision occurs when there is only one differentiated process

A There are

THREE TYPES OF TRICHROMASY

- 1 *Normal color vision*
- 2 *Anomalous, manifesting relative deficiencies in one of the processes but requiring three primaries to match all the spectral colors*
- 3 *Low discrimination, manifesting poor discrimination in many or all colors but still requiring three primaries*

The definitive characteristic of the subject with trichromatic color vision is that he requires a mixture of at least three primaries to match any or all colors *He cannot match all colors with less than three primaries* He makes three kinds of discrimination light-dark, yellow-blue and red-green (Hering's classification) If the amounts of the primaries he uses in making the match are normal, or nearly so, he is said to have normal color vision If his first (*proto*) color process (*red component*) is weak, he will be relatively insensitive to red and is said to have *protanomalous trichromatic color vision* If his second (*deutero*) color process (*green component*) is weak, he will be relatively insensitive to green and is said to have *deuteranomalous trichromatic color vision* A rare type is the subject with *tritanomalous trichromatic color vision*, who is relatively insensitive in the third (*tito*) color process (*violet or blue component*) If he makes serious and widely scattered errors with all colors, it is assumed that all three primaries are depressed sufficiently to amount to a defect and he is classified as having "*low discrimination*"

B There are

THREE TYPES OF DICHROMASY

- 1 *Protanopia* (first process gone—formerly called “red blindness”)
- 2 *Deutanopia* (second process gone—formerly called “green blindness”)
- 3 *Tritanopia* (third process gone—formerly called “violet [blue] blindness”)

The distinctive feature of the subject with dichromatic color vision is that *he can match all the spectral colors with only two primaries*—hence the term “di-chromatic.” He can make only two kinds of visual discrimination—light-dark and either blue-yellow or red-green, usually the former.

To the *protanopic* subject the spectrum in the extreme red appears very dark (in other words, his spectrum is shortened at the long wave end), and he finds a neutral band in the blue-green, which appears to him abnormally light. To the left of this neutral band the spectrum appears to him as yellow of varying chroma and brightness, to the right, as blue of varying chroma and brightness. The *protanopic* subject has a neutral band also in the red of the normal color system, just too purplish to be a spectral red.

To the *deutanopic* subject the spectrum appears of about the same brightness as it does to the normal observer, and he finds a neutral band in the green. To the left of this neutral band the spectrum appears to him as yellow of varying chroma and brightness, to the right, as blue of varying chroma and brightness. The *deutanopic* subject has a neutral band also in the red-purple of the normal color system, outside the limits of the visible spectrum.

The *tritanopic* subject finds neutral bands in the green-yellow of the spectrum and in the violet close to the extreme end of the spectrum. Between these neutral bands he sees green of varying chroma and brightness, and to the left of the neutral band in the green-yellow, red of varying chroma and brightness. This type of dichromasy is rare, and its characteristics are not as well known as are those of the other dichromatic types.

C An observer possessing *monochromatic* vision is capable of light-dark discrimination only. He has no chromatic discrimination.

Stated in another way, it may be said that there are

THREE MAIN TYPES OF ABNORMAL COLOR VISION.

- 1 *Anomalous trichomasy*
- 2 *Dichomasy*
- 3 *Monochomasy*

Persons with *anomalous trichomasy* require a mixture of *three* primaries to produce all the colors they are capable of experiencing,

but they utilize anomalous proportions of the primaries. The two more common types of this defect are the *protanomalous* (predominantly red weak) and the *deutanomalous* (predominantly green weak). A rare type is the *tritanomalous* (predominantly violet weak). Like the person with normal trichromasy, the seeing of persons with anomalous trichromasy includes light-dark, blue-yellow and red-green discriminations.

Persons with *dichromasy* are protanopic (formerly called "red blind"), deutanopic (formerly called "green blind") or tritanopic (formerly called "violet [blue] blind"). They match all colors with *two* primaries.

Persons with *monochromasy* have no chromatic discrimination and match all colors by varying the amount (lightness or darkness) of *one* primary. They are totally color blind (achromatopsia).

There are

THREE PSYCHOPHYSICAL FACTORS IN THE COLOR OF THE TEST MATERIALS

- 1 *Dominant wavelength*
- 2 *Luminous reflectance*
- 3 *Purity*

Each of these psychophysical factors must be controlled by suitable adjustment of the test material, because they have a very critical effect on the responses to the test. A change of one psychophysical factor frequently involves a change in all three attributes of the psychologic perception, although change in dominant wavelength chiefly affects the hue of the perception, change in reflectance chiefly affects the lightness, and so on. Much color testing material is worthless because of the critical influence of these three factors, since there are

THREE PSYCHOLOGIC ATTRIBUTES OF COLOR PERCEPTION

- 1 *Hue*
- 2 *Lightness* (closely correlating with Munsell value)
- 3 *Saturation* (closely correlating with Munsell chroma)

A change in one psychophysical factor may change the psychologic perception of the other factors or of the test situation. The psychologic, psychophysical and physical factors are roughly correlated in the following tabulation.

Psychologic Term	Quasipsychologic Term	Psychophysical Term	Physical Term
Hue	Munsell hue	Dominant wavelength	Spectral centroid
Lightness (brightness)	Munsell value	Luminous reflectance	Area under the spectral curve
Saturation (depth of color)	Munsell chroma	Purity	Narrowness of spectral curve

II. THE ICI COORDINATE SYSTEM AND STANDARD OBSERVER

The *ICI Coordinate System* is a graphic system of plotting various colors in their relation to each other. It is based on the proportion of three imaginary primaries (red, green and blue) required by the *ICI Standard Observer* to match all wavelengths of the visible spectrum. The ICI Standard Observer, as defined in section I, is an imaginary physiologic entity whose color responses have been computed from data supplied by carefully trained normal observers. The data take the form of three columns of figures (or curves), which, when reduced to coefficients or percentages, may be plotted on the ICI Coordinate System as a curve representing the locus of all the colors of the visible spectrum. Most color stimuli used in accurate color testing are now plotted on the ICI diagram and specified in terms of ICI coordinates or are given in the Munsell color notation. (Most of the Munsell colors have been given ICI Coordinate System notations.) For color work in the United States it is usual to use ICI Illuminant C as the standard illuminant, since it represents daylight conditions. (In Great Britain it is usual to use ICI Illuminant B as the standard—noon sunlight.)

The ICI diagram is useful for studying the colors confused by an observer with defective color vision. For example, Pitt has determined the chromaticity confusions for protanopic and deuteranopic dichromatic systems and has plotted them on the ICI diagram. The zones which lie between the confusion lines shown in the diagram represent areas of the ICI diagram for a given lightness or brightness level within which the dichromatic subject makes no distinction. From zone to zone there is for him a distinguishable difference in hue or saturation or both. The chromaticity confusion lines converge to the vicinity of a point for each of the two common types of red-green blindness. Pitt has also plotted on this diagram the position of 43 colors extensively used in the paint trade. Broadly speaking, the subject with dichromatic vision can distinguish two colors only if they occur in different zones. From his diagram it is seen that the subject with deuteranopic vision can distinguish only 15 of these 43 colors, and the subject with protanopic vision, only 12. If 500 different trichromatic colors were listed, the number distinguishable to the subject with dichromatic color vision would only slightly increase and could never be greater than about 28 for the deuteranopic and 18 for the protanopic subject for a 2 degree field.

III. THE ISCC TEST DATA

For several years the Inter-Society Color Council (ISCC) has been interested in developing tests for color blindness and color aptitude. Its Color Blindness Test Committee has actively assisted in evaluating

old tests, evaluating test materials and producing new tests and new materials. The Single Judgment Test for Red-Green Discrimination, devised by the committee, is one such test. Other tests are being critically studied for their value both as screening tests (to separate observers with normal from those with defective color vision) and as diagnostic tests (to classify observers with defective color as to type and extent of defect).

Among recently devised tests are

- 1 *The Farnsworth-Munsell 100-Hue Test*
- 2 *The Farnsworth Dichotomous Test*
- 3 *A simplified form of anomaloscope suitable for office use*
- 4 *The Hardy-Rand-Rittler Polychromatic Plates*

Typical profiles obtained with the 100-hue Test, and the Dichotomous Test have been obtained for subjects with anomalous trichromasy and subjects with dichromasy of all three types and for observers having low color discrimination.

The Rand Anomaloscope—This is designed to give a quick determination analogous to the Rayleigh equation (the ratio lithium red to lithium green required to match sodium yellow). The anomaloscope was originally designed by Nagel to distinguish between normal trichromasy and anomalous trichromasy. It also offers a ready differentiation between protanopic and deuteranopic color vision and a diagnosis of low color discrimination for red and green. For the last determination the just noticeable difference in hue between yellow and yellow-green and between yellow and yellow-red is measured.

The Hardy-Rand-Rittler Polychromatic Plates—These plates are designed to diagnose both type and degree of defect in color vision for both red-green and blue-yellow. Each plate consists of a white background in which are countersunk small disks of Munsell neutral gray of different sizes and values, and small disks of Munsell color of predetermined hue and different sizes and values. The color disks form geometric patterns which can be presented in different positions to provide an objective check on the color discrimination and to prevent coaching. There are four series of plates. In each plate of *series A* the patterns are presented in a given chroma of the red most difficult for the subject with the predominantly red-defective (protanopic) type and the red-purple most difficult for the subject with the predominantly green-defective (deuteranopic) type of red-green deficiency to distinguish from gray, in *series B*, in a chroma of the blue-green most difficult for the subject with the predominantly red-defective type and the green most difficult for the subject with the predominantly green-defective type of red-green deficiency to distinguish from gray, in *series C*, in a

chroma of the green-yellow most difficult for the subject with the predominantly violet-defective (tritanopic) type and the yellow most difficult for the subject with the predominantly blue-defective tetrachromatopic—G E Mullen) type of blue-yellow deficiency to distinguish from gray, and in series D, in a chroma of the violet most difficult for the subject with the predominantly violet-defective type and the blue most difficult for the subject with the predominantly blue-defective type of blue-yellow deficiency to distinguish from gray. In the successive plates of each series the color patterns appear in increasing steps of chroma. The degree of defect is evaluated by the number of failures and their chroma distribution, and the type of defect, by the hue discriminated most poorly.

In our experimental work the results of the aforementioned tests have been compared with those given by the Ishihara Tests for Colour-Blindness (fifth, seventh and ninth editions), the Rabkin Polychromatic Plates for Testing Colour Vision and the American Optical Company's Pseudo-Isochromatic Plates for Testing Color Perception. In our opinion, the first of these tests (Ishihara) is good for screening the observer with defective red-green vision from the observer with normal vision, but it fails to differentiate adequately between protanopic and deuteranopic subjects, between protanomalous and deuteranomalous subjects and between subjects with anomalous trichromatic and those with dichromatic vision. The second of these tests (Rabkin) also can be relied on to screen the subjects with defective red-green vision from the subjects with normal color vision. In addition, it differentiates well between protanopic and deuteranopic subjects and between protanomalous and deuteranomalous subjects but does not adequately separate subjects with anomalous trichromatic vision from those with dichromatic vision. It has two plates designed to test blue-yellow deficiency, but these are not entirely adequate for the purpose. The third of the aforementioned tests (the American Optical Company's selection) comprises in one series certain of the Ishihara plates and certain of Stilling's Pseudo-Isochromatic Plates for Testing the Color Sense. The color reproductions are frequently inaccurate. Only tests of red-green deficiency are included. Like the Ishihara test, this series fails to differentiate between the different types of red-green deficiency and between anomalous trichromasy and dichromasy. However, a certain error score in a selected series of the more significant plates can be used to indicate a red-green defect. These three tests have been critically evaluated, and several reports have been published¹

1 Hardy, LeG. H., Rand, G., and Rittler, M. C. Tests for Detection and Analysis of Color Blindness. I. An Evaluation of the Ishihara Test, *Arch Ophth* **34** 295 (Oct.) 1945, II. Comparison of Editions of Ishihara Test, *ibid* **35** 109 (Feb.) 1946, III. The Rabkin Test, *ibid* **35** 251 (March) 1946.

IV TYPICAL TESTS IN CURRENT USE

A SORTING TESTS

WOOLS—Holmgren, Jennings, Oliver, Thomson, Murray, Nela and others (*not standardized, no quantitative score, no light standard, poor administration, changes in color, not sensitive for detection of anomalous subjects*)

BEADS—Edridge-Green (*results difficult to interpret, many loose parts, colors not standardized*)

CARDS—Philip (*more useful for detection of color weakness than color blindness, many loose parts, no standard illuminant*)

B MATCHING TESTS

Nagel anomaloscope (*Rayleigh Equation—sodium, thallium and lithium lights Technical difficulties, inconvenient, inaccessible*)

Rand anomaloscope (*in production stage*)

Collins' papers (*variable, Biedley papers, loose parts, no standard illumination*)

ISCC chips—(*time consuming, various modifications under study*)

ISCC aptitude test—(*time consuming, various modifications under study*)

C NAMING TESTS

LANTERNS—Edridge-Green lantern, Williams lantern and others (*These are luminous signal tests They need to be evaluated with reference to reflected signal tests All luminous signal tests are dependent on source and outside illumination They utilize small test objects, which yield small retinal images with high retinal brightness*)

New lanterns are being developed in the Royal Canadian Air Force and the United States military services

D DISCRIMINATION AND SENSITIVITY TESTS

Filters, spectrometers (*laboratory instruments, inaccessible, inconvenient, require standardization*)

Houston filters (*laboratory apparatus, good for special work*)

Nagel cards (*use of color names required, no standard illuminant, time consuming*)

Pseudoisochromatic plates

Stilling (*illuminant not standardized, complicated instructions, no exact diagnosis*)

Ishihara (*good rough screening test, no exact diagnosis; score not indicative of degree of defect*)

Rabkin (*with proper illuminant and administration, good practical test for screening and classification*)

- American Optical Company selection (*poor selection of plates, reproductions frequently inaccurate, no critical score*)
- Hardy-Rand-Rittler (*illumination and colors standardized, test planned for screening plus qualitative plus quantitative diagnosis, in production*)

E HUE AND CHROMA SERIES ARRANGEMENT

- NIIP Discs (*used in England for color aptitude testing*)
- Murray's Cards (*promising test, in research stage*)
- Farnsworth-Munsell 100-Hue Test (*excellent test, many loose parts, complicated scoring, qualitative but not quantitative classification*)
- Farnsworth Dichotomous Test (*excellent for qualitative classification of extreme defects, loose parts, does not screen persons with weak defective color vision from those with normal color vision*)

V. A CLASSIFICATION OF TYPES OF COLOR VISION

•NORMAL COLOR PERCEPTION

- 1 NORMAL TRICHROMASY (*three primaries, normal mixtures Discriminates light-dark, yellow-blue, red-green*)
 - h—high or excellent color preception
 - m—medium or average color preception
 - l—low or poor color perception, not sufficient to be called defective Approaches low discrimination type of defect

DEFECTIVE COLOR PERCEPTION

- 1 LOW DISCRIMINATION (*depression of all three primaries sufficient to amount to a defect*)
 - x—mild (approaches low normal)
 - y—medium
 - z—marked (approaches monochromasy)
- 2 ANOMALOUS TRICHROMASY (*three primaries, anomalous mixtures*)
 - (a) Protanomalous (*defective red sensitivity, narrowed luminosity curve Discriminates light-dark, yellow-blue, red-green poorly*)
 - x—mild
 - y—medium
 - z—marked (approaches dichromasy, protanopia)
 - (b) Deuteranomalous (*defective green sensitivity, normal luminosity curve Discriminates light-dark, yellow-blue, red-green poorly*)
 - x—mild
 - y—medium
 - z—marked (approaches dichromasy, deuteranopia)

(c) *Tritanomalous* (defective violet sensitivity, normal luminosity curves [?]) Discriminates light-dark, red-green, yellow-blue poorly)

3 **DICHROMASY** (two primaries)

(a) *Protanopia* (first process gone, formerly called "red blindness", shifted luminosity curve, neutral points at 493 millimicrons and 493 c)

p—pure type (discriminates light-dark, yellow-blue)

q—complicated type (discriminates light-dark, yellow-blue poorly)

(b) *Deutanopia* (second process gone, formerly called "green blindness", no shift in luminosity curve, neutral points at 497 millimicrons and 497 c)

p—pure type (discriminates light-dark, yellow-blue)

q—complicated type (discriminates light-dark, yellow-blue poorly)

(c) *Tritanopia* (third process gone, formerly called "violet blindness", no shift in luminosity curve [?], neutral points at 572 millimicrons and 572 c)

p—pure type (discriminates light-dark, red-green)

q—complicated type (discriminates light-dark, red-green poorly)

4 **MONOCHROMASY** (one primary, no hue discrimination, "total color blindness—achromatopsia", discriminates light-dark)

TRANSPLANTATION OF HUMAN VITREOUS

A Preliminary Report

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I HAVE not been able to discover any references in the literature to the transplantation of human vitreous from the eye of one person to the eye of another person. It is believed that the cases reported here are the first recorded instances of this procedure. This report is based on some as yet unpublished experiments on transplantation of vitreous in animal eyes.

HISTORICAL REVIEW

Although there are no reported cases of the transplantation of human vitreous, there have been various attempts to provide a clearer vitreous by other methods.

In 1890 Ford¹ withdrew vitreous from several eyes, the loss being made up by the aqueous. He reported improvement in visual acuity from perception of light to 20/60 in 1 case. Deutschmann,² in 1906, reported on the injection of vitreous from calf and rabbit eyes into human eyes for the treatment of detachment of the retina. Of 67 patients the condition of 26 was purportedly improved and that of 38 was unimproved. Komoto,³ in 1910, reported on the withdrawal of vitreous and injection of saline solution, and Elschnig,⁴ on the injection of air. The results of similar procedures were reported by a number of authors between 1920 and 1930, notably by zur Nedden⁵ in 300 cases of withdrawal of vitreous.

It was decided to transplant clear vitreous into the eyes of patients with persistent and unabsorbed hemorrhage in the vitreous who had normal intraocular tension and good light projection. Two of the patients had had injuries to the eyes, and 1 had apparently had a spontaneous hemorrhage.

1 Ford, V. Proposed Surgical Treatment of the Opaque Vitreous, *Lancet* 1 462, 1890.

2 Deutschmann, R. Zur operativen Behandlung der Netzhautablosung, *Klin Monatsbl f Augenh* 4 364, 1906.

3 Komoto. Ueber Glaskorperwaschung bei unheilbarer Glaskorperblutung, abstracted, *Klin Monatsbl f Augenh* 50 265, 1912.

4 Elschnig, A. Ueber Glaskorperersatz, *Ber u d Versamml d deutsch ophth Gesellsch*, 1911, p 514.

5 zur Nedden. The Curative Value of Aspiration of the Vitreous, *Arch, Ophth* 57 109 (March) 1928.

PROCEDURE

With the patient under sodium pentothal anesthesia, the sclera is exposed in the selected quadrant through a conjunctival incision, and a small incision is made with a cataract knife in the equatorial region between a previously placed 0000 silk mattress suture. An 18 gage needle on a 5 cc syringe is introduced into the vitreous chamber under direct observation by the assistant. Approximately 1.5 cc of vitreous is withdrawn and the syringe then detached. A syringe containing approximately 2 cc of clear vitreous from an eye enucleated a few minutes before and kept in an incubator at 37 C is then attached to the needle. While the assistant exerts tension on the partially tied suture, the vitreous is injected until the eye has reformed. The needle is quickly withdrawn and the suture pulled up, and the tie is completed. Atropine sulfate, 1 per cent, is instilled and a binocular dressing applied.

POSTOPERATIVE TREATMENT

Mild sedatives are used as indicated for two nights, and codeine and acetylsalicylic acid suffice for control of pain. The patient is kept on his back with a pillow for two days, after which he is allowed to turn and be elevated. He is permitted to be up on the fourth or fifth day. There has been no postoperative discomfort. Two patients had a ring of diathermy punctures made at the operative site approximately two weeks prior to transplantation with the idea of stimulating the formations of scar tissue to prevent detachment of the retina. Although this has not been done in all cases, it is believed to be a worth while precaution.

The reports of 3 cases of transplantation of the vitreous follow.

REPORT OF CASES

CASE 1—*Recipient I I H Negro, blood group O*

Note on Admission. The patient gave a history of "spots" before the left eye with recurrent visual loss at various times for two years. On June 9, 1944, while taking physical training, he noticed sudden loss of vision in the left eye. Visual acuity in this eye was reduced to perception of light. He was treated at a station hospital from June 9 to July 19, when he was transferred to the Army general hospital with which I am associated.

Examination. Right eye. The eye was normal throughout. Vision was 20/20.

Left eye. The external condition was normal. Ophthalmoscopic examination revealed a black reflex, no details of the fundus were visible. Examination with the slit lamp showed that the anterior chamber and the lens were normal, the vitreous was filled with a great many golden brown particles, suggestive of hemorrhage. Vision was limited to perception of light, projection was excellent.

Diagnosis. A diagnosis of spontaneous hemorrhage in the vitreous was made. A complete survey revealed nothing of significance except for syphilis, for which the patient was under treatment. He was returned to duty Sept 9, 1944.

On Jan 6, 1945 the patient was readmitted to the hospital. He had not noticed any change in vision since his discharge. Vision was 20/20 in the right eye and was limited to perception of light, with good projection, in the left eye. The tension was 18 mm in each eye.

Donor J O F Age 27, white, blood group A

Note on Admission. The patient was wounded in action June 30, 1944 by shell fire. He was admitted to this Army hospital Nov 2, 1944. He gave no previous history of ocular trouble.

Examination Right Eye There was dense corneal opacity with a staphyloma over the lower three fifths of the cornea. Tension was 3+. Vision was limited to light perception, with faulty projection.

Left eye The eye was normal. Vision was 20/30 without correction.

Diagnosis The diagnosis was secondary glaucoma of the right eye. Enucleation was advised because of poor light projection and the unsightly eye.

Operation—On Feb. 19, 1945, with the patient under sodium pentothal anesthesia, the left eye was enucleated, and a basket type implant used. The eye was placed in isotonic solution of sodium chloride at a temperature of 37 C. On an adjoining table, the left eye of patient I V H was prepared and the lower temporal quadrant of the sclera exposed. According to the previously described procedure, 2 cc of vitreous was then withdrawn from the donor eye through an 18 gage needle into a 5 cc syringe. This was placed in an incubator at body temperature. Through an equatorial incision in the recipient eye, 1.5 cc of straw-colored vitreous was withdrawn, using a similar needle and technic. The syringe was removed from the needle and replaced with the syringe containing donor vitreous, which was slowly injected. The globe, which had become folded in with the withdrawal of vitreous, now reformed. The needle was withdrawn while the assistant pulled up the suture, which was then tied and cut. The conjunctiva was closed with 0000 interrupted surgical gut. Atropine sulfate, 1 per cent, was instilled and a binocular dressing applied.

Postoperative Course—The eye was redressed on the third postoperative day, and 2 per cent atropine sulfate was instilled. There was little reaction.

February 25 No unusual reaction followed transplantation of the vitreous. The vitreous showed considerable clearing. The disk was seen indistinctly, and a number of the diathermy punctures were also visible. Vision had improved to perception of hand movements at 2 feet (60 cm).

February 27 The details of the fundus could be made out in the section of the periphery extending approximately from 9 to 3 o'clock. On the temporal side there was a small retinal hemorrhage at about 2:30 o'clock. The disk could not be seen, although it was visible two days after the operation. Tension was 19 mm in the right eye and 9 mm in the left eye.

March 1 The disk could be distinguished clearly, as well as the arteries and veins in the midperipheral area below and in the region of the macula. The extreme periphery above and temporally could be seen, as noted in the previous examination. There was a very slight reaction remaining.

March 2 Tension was 15 mm in the right eye and 11 mm in the left eye. The fundus was unchanged.

March 7 Tension was 18 mm in the right eye and 13 mm in the left eye. The posterior pole of the fundus remained visible. Apparently, the fresh vitreous had diluted some of the old, opaque vitreous, to give a somewhat hazy view of the posterior pole. The macular area was visible as a dark reddish spot, with the appearance of an old degeneration.

March 21 Tension was 19 mm in the right eye and 14 mm in the left eye. The eye was quiet. The vitreous remained moderately clear.

April 18 Tension was 17 mm in the right eye and 16 mm in the left eye. Vision in the left eye was 20/200, with the pinhole disk it was 20/70+, and the patient read Jaeger test type 10.

May 3 The media remained clear. The disk and the areas previously noted were well seen, as was the dark area in the macula. Vision in the left eye

was 20/100, with—1 00 D cyl, axis 180 it was 20/60—1 Tension was 17 mm in each eye

The patient was discharged to duty June 6, 1945

The patient was seen in the clinic on September 28 At this time the tension was 17 mm in each eye The left eye was white and quiet Ophthalmoscopic examination of this eye showed some floaters, but no more than on previous examinations The disk, the vessels and the macular area were distinct The periphery was clearly seen except below, where some remnants of old hemorrhage were present in the vitreous Vision was 20/100 in each eye, with —1 00 D cyl, axis 180 it was 20/60—1

Comment—No unusual reaction was evident postoperatively The eye showed only a slight conjunctival injection, equivalent to what is sometimes seen after discission of a secondary membrane Examination with the slit lamp showed no evidence of iritis The tension became normal approximately one month later The vitreous showed considerable clearing during the first few days, and the area of clear vitreous became greater during the first month Vision became stabilized at the end of two months The improvement was still present seven months after operation From the appearance of the vitreous it was felt that vision would be considerably better if it were not for the macular change

CASE 2—Recipient A F H Age 23, white, blood group O

Note on Admission The patient was involved in a fist fight on Dec 25 1944, when he was struck in the left eye and lost consciousness Examination at an overseas hospital on December 29 revealed that vision was 20/20 in the right eye and limited to light perception in the left eye, with proptosis and hemorrhage into the anterior chamber The tension was elevated While he was under treatment, the hemorrhage of the anterior chamber absorbed, revealing a remaining hemorrhage in the vitreous The patient was examined at this Army hospital on Feb 17, 1945

Examination Right eye The eye was normal throughout

Left eye The external condition was normal The fundus gave a black reflex Examination with the slit lamp revealed a large amount of mobile blood pigment in the vitreous Vision was 20/20 in the right eye and was limited to light perception in the left eye Tension was 15 mm in the right eye and 16 mm in the left eye Roentgenographic examination revealed no foreign body

Diagnosis The diagnosis was post-traumatic hemorrhage of the vitreous

Course Examination on March 8 revealed a small amount of red blood in the extreme lower part of the fundus

Donor W E A Age 25, white, blood group O

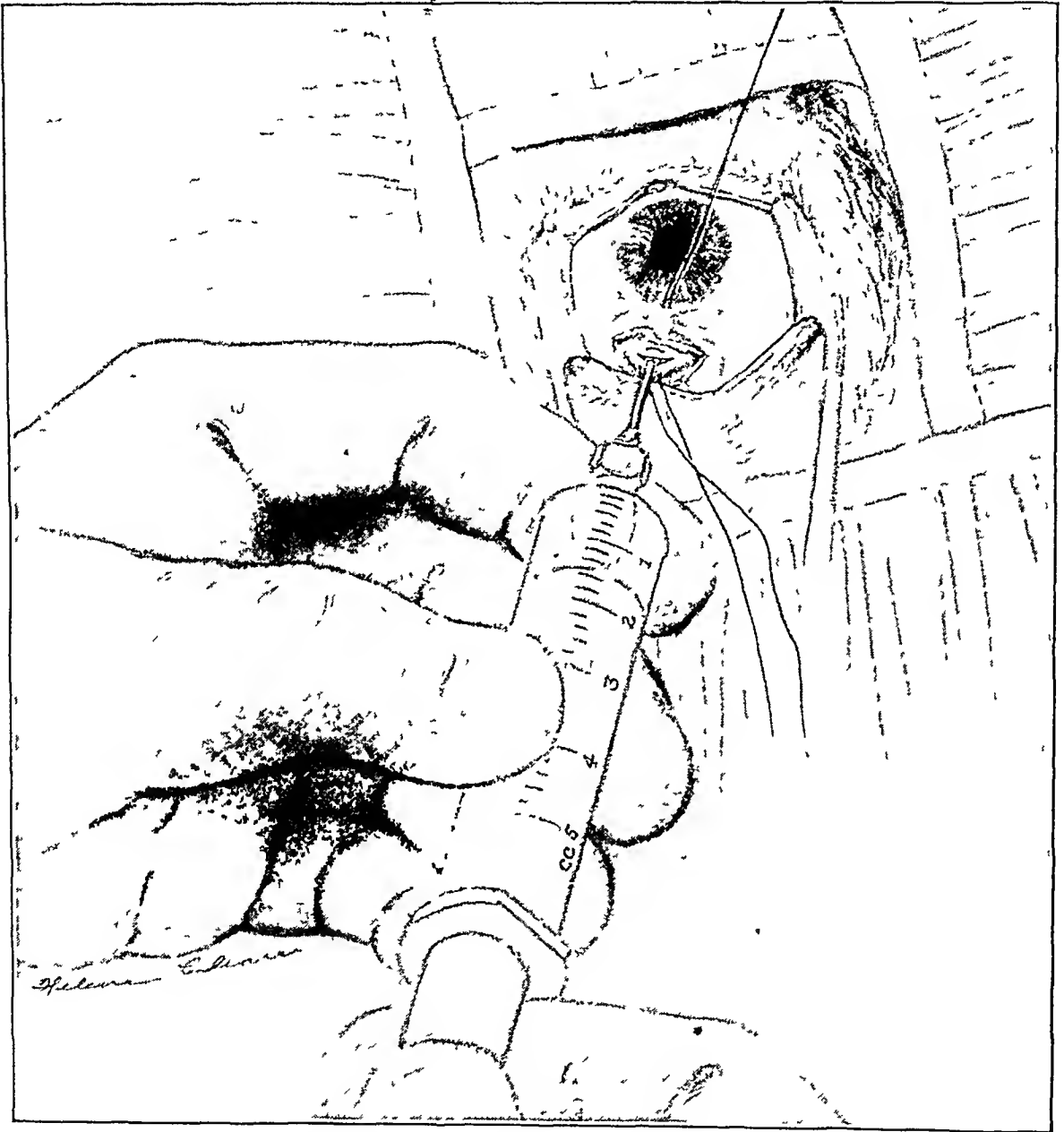
Note on Admission The patient had been hit in the left eye with BB shot at the age of 9 years, after which he had some type of operation and later lost the sight of the eye

Examination Right eye The eye was normal throughout

Left eye The cornea was thick and somewhat opaque The anterior chamber was very shallow, with a dense pupillary membrane Tactile tension was normal Vision was 20/20 in the right eye and was limited to light perception, with faulty projection, in the left eye

Diagnosis The diagnosis was occlusion of the pupil and possible detachment of the retina in the left eye

Operation—On March 9, 1945 a transfusion of 2 cc of vitreous was attempted. However, no vitreous could be withdrawn through a 15 gage needle. On withdrawal of the needle some clear vitreous escaped, and approximately 15 cc of vitreous was injected into the recipient eye from the donor eye of W E A, enucleated prior to the transplantation of vitreous.



Withdrawal of cloudy vitreous (15 cc)

Postoperative Course—March 12 A small amount of fresh hemorrhage was noted on the lower pupillary border. Tactile tension was normal. There was moderate injection of the bulbar conjunctiva. There was also evidence of additional fresh hemorrhage in the anterior vitreous, below. A vessel could be seen on the temporal side, suggestive of detachment of the retina.

March 21 Tension was 17 mm in the right eye and 20 mm in the left eye. The vitreous still had a large amount of mobile blood. Vision was limited to perception of hand movements at 6 feet (180 cm). Projection was poor on the temporal side.

The patient was discharged from the hospital on Aug 26, 1945.

Comment—There was the impression at the operation that the needle did not penetrate into the vitreous chamber, but remained behind the retina, and that the patient probably had a retinal detachment. This impression was strengthened by the loss of clear, fluid vitreous, rather than cloudy vitreous, when the needle was withdrawn. The fact that the patient had further hemorrhage after operation suggested that the vascular structure of the eye was not in a healthy condition. The injection of vitreous probably increased the detachment. At the time of the patient's discharge the eye was entirely quiet. There was no evidence of fresh hemorrhage. The tension was normal. Unfortunately, the light projection, which was not good after operation, had not been recorded before operation. The procedure, however, was a complete failure.

CASE 3—*Recipient W S Age 27, white, blood group A*

Note on Admission The patient stepped on a land mine in France on Aug 29, 1944 and was injured in both eyes, the legs, the right arm and the chest. The right eye was enucleated shortly after injury. It was noted at an overseas hospital, on September 2, that there was some red blood in the vitreous chamber of the left eye. The patient was examined at this Army hospital on Nov 17, 1944.

Examination The right eye had been enucleated.

Left eye Vision was 20/300. Small maculas and foreign bodies lay on the surface of the cornea. A corneal scar was present at 2 o'clock, with some embedded debris. A complete iridectomy of the upper temporal quadrant had been performed. The anterior chamber was of normal depth. The pattern of the iris was well preserved. The pupil reacted to light. There was a slight capsular opacity of the lens posteriorly. Ophthalmoscopic examination revealed a dense vitreous opacity occupying all but the extreme upper periphery, where the vessels could be hazily seen.

Diagnosis The diagnosis was hemorrhage of the vitreous, and transplantation of vitreous was suggested.

Donor B D N Age 28, white, blood group O

Note on Admission The patient was struck in the left eye on Nov 8, 1944, resulting in a penetrating wound of the left globe. Vision was limited to perception of hand movements. He was seen in this Army hospital on December 13.

Examination Right eye The eye was entirely normal.

Left eye Inspection showed a healed laceration of the lids with slight ptosis. There was a dense leukoma of the cornea, with a disorganized iris adhering to it. The lens was cataractous. The fundus could not be seen.

Vision was 20/50 in the right eye (20/15 with correction) and was limited to perception of hand movements at 1 foot (30.4 cm), with poor projection, in the left eye.

Diagnosis The diagnosis was occluded pupil, cataractous lens and possible retinal detachment.

Operation—On April 12, 1945 vitreous was withdrawn from the recipient eye through a temporal incision at the site of the diathermy punctures, and approximately 2 cc of vitreous was injected from the donor eye of B D N

Postoperative Course—April 18 The slight ciliary flush, which had been present for three days, had practically disappeared. A good red reflex was visible over the upper one half to two thirds of the fundus, and retinal vessels could be clearly seen in the macular area and one half of the disk itself. The tension was low.

April 20 The disk could be seen fairly well, although the media was slightly hazy. There was a large vitreous floater which temporarily obscured vision when the patient moved the eye suddenly.

During the following three weeks the eye became entirely white. The tension gradually improved, and the upper half of the fundus could be seen fairly well.

May 15 Tension was 12 mm.

May 31 Vision was 20/40, with a -1.00 D sphere it was 20/20—2. There was considerable cloudy vitreous in the lower two fifths of the fundus.

July 13 Vision was 20/40 and was correctible to 20/20. Tension was 13 mm. The details of the fundus in the upper temporal quadrant were visible well out into the periphery, as well as in the macular region. The details could also be seen well down the temporal side to 4 o'clock. On examination with the slit lamp the cornea, the anterior chamber and the iris appeared as they had on admission.

August 4 The fundus was unchanged except for the gradual clearing of the vitreous below on the temporal side. An opacity remained in the lower nasal quadrant of the vitreous. No lesion was evident in the fundus except for the hemorrhage in the vitreous and a choroidal scar, which could be seen in the upper temporal quadrant at the site of injection. Vision was 20/40 in the left eye, with -0.50 D sph -0.50 D cyl, axis 155 it was 20/20. Tension was 13 mm.

The patient was discharged from the hospital and from the Army on Aug 6, 1945.

Comment—This patient was on the program for the blind and was scheduled to continue his rehabilitation training. However, because of his improved vision, he was discharged directly to his home. The visual field was very good except for the opacity below, which interfered slightly with his vision on sudden movement, to such an extent that it was not possible at the time of his discharge to drive a car. However, he was able to read Jaeger type 1, read the newspapers and carry on his correspondence and had no difficulty in traveling about wherever he wanted to go.

SUMMARY

Approximately ten years ago I conducted some experiments on laboratory animals, which have not yet been published. These experiments demonstrated that the transplantation of vitreous from the eye of one animal to that of another of the same species is a safe and practicable procedure. Publication was delayed until an opportunity should present itself to conduct this procedure on suitable human eyes.

It is well known that the absorption of a hemorrhage in the vitreous may sometimes be long delayed, but after many months it will clear remarkably. In other cases retinitis proliferans with vitreous bands and adhesions will develop, with disastrous results to the eye. Whether transplantation should be tried early or late is difficult to decide. Probably in cases of severe hemorrhage the earlier a vitreous transplantation is done after bleeding stops, the better. It so happened that the only cases available in this Army hospital have been those of old hemorrhage into the vitreous chamber. It is possible that further absorption of these hemorrhages would have taken place if nothing had been done. However, it is a not uncommon experience to see retinitis proliferans develop within a short time.

In all cases in which this procedure was used it was discussed with the patients, and it was explained to them that this was an experimental and untried method so far as human eyes were concerned. They all expressed a desire to have the operation.

In no cases in which the operation has been done has the eye been lost or apparently become worse than it was before operation. Further investigation is under way, but much still remains to be done. This applies to the actual operative procedures as well as to the type of cases selected. In a case of hemorrhage in the vitreous one is working very much in the dark, and further knowledge is necessary in order that one may be able to determine which cases are suitable and when operation should be performed. This implies a study and correlation of the clinical appearance and the pathologic changes together with chemical studies on the abnormal vitreous. The possibilities of this procedure in treatment of other conditions, such as detachment of the retina, are still to be investigated. Repeated transplantations of vitreous have not yet been done.

One cannot, of course, introduce instruments into the vitreous chamber with impunity, but it is felt that the procedure described here should open up a new field for surgery in selected cases in which the treatment until now has been, to say the least, expectant.

The observations on the 3 cases reported may be summarized as follows:

In 2 of 3 cases in which transplantation of vitreous was done, the procedure was successful up to the time of this report.

From 1.5 to 2 cc. is the maximum amount of vitreous which can be withdrawn through a 15 or 18 gage needle from the recipient eye.

The blood group does not appear to be significant.

There was a decided reduction in the opacity of the vitreous in the cases in which the operation was successful.

The pathologic vitreous appeared to be more fluid than normal, but it was not possible to determine whether it became more fluid with the admixture of transplanted vitreous

There was a moderate reaction after the procedure, but no evidence of a foreign protein reaction was noted

The tension in all 3 cases returned to normal within a reasonable period and remained normal

The procedure was successful in cases of spontaneous as well as of post-traumatic hemorrhages in the vitreous

SUPRASELLAR MENINGIOMAS ASSOCIATED WITH SCOTOMATOUS FIELD DEFECTS

N S SCHLEZINGER, M D

BERNARD J ALPERS, M D

AND

B P WEISS, M D

PHILADELPHIA

SUPRASELLAR meningiomas are associated in typical instances with atrophy of one or both optic nerves and bitemporal hemianopsia, with or without changes in the sella turcica and with or without symptoms of endocrine disturbance. In some circumstances, optic nerve atrophy may be minimal or altogether absent the only evidence of chiasmal compression being a bitemporal hemianopsia for form or color or both. In almost all instances, the symptoms are slowly progressive, with visual loss prominent and headache equally disabling.

Not sufficiently well recognized as part of the suprasellar tumor syndrome is the occurrence of sudden visual loss with scotomas in the visual fields, associated with more or less prominent headache. The development of symptoms may be so rapid and may simulate so closely in the early stages the clinical picture of retrobulbar neuritis that great care must be exercised to avoid discarding a diagnosis of suprasellar meningioma. For this reason, we believe it is desirable to report our experience with 4 cases which illustrate the points in question.

REPORT OF CASES

CASE 1—A woman aged 31 admitted on Sept 16, 1939, with history of failing vision for eight months, including period of partial remission, bilateral atrophy of optic nerve with central scotoma in left eye and a combined central and peripheral field defect in right eye, progression, with severe headaches for a year prior to death, on April 19, 1942, after operation. Verified diagnosis of suprasellar meningioma.

History—E H, a woman aged 31, was admitted to the Wills Hospital on Sept 16, 1939, to the service of Dr Louis Lehrfeld. The family history was noncontributory. The past medical history revealed that the patient gained weight excessively during her first pregnancy, which resulted in a miscarriage, and that she was underweight and anemic during her second pregnancy, which terminated, in 1935, in prolonged labor, followed by delayed extraction of the placenta. Some irregularity in menstruation and a sense of numbness in the arms and legs were experienced during 1938, an abscessed tooth was treated in January 1939.

From the Department of Neurology, Jefferson Medical College of Philadelphia

The present illness developed suddenly in February 1939, when the patient, after looking out of a window at ground covered with snow, noticed impairment of vision. She became panicky and depressed. The visual impairment became progressively worse, so that a month later she could only see objects within several feet of her. Treatment, including medication in the form of parenteral injections of thiamine hydrochloride, was followed by gradual improvement in vision, so that by June 1939 visual acuity was 20/100 in the left eye and 20/50 in the right eye. This condition continued for about one month and then gradually regressed. The patient became increasingly apprehensive and also manifested emotional instability in the form of crying. She complained of "flakes of light" in both eyes.

Examination—On admission the patient appeared rather poorly nourished, her heart, lungs and abdomen were grossly normal.

Neurologic examination revealed the station to be within normal limits. The ordinary gait was normal, but there was unsteadiness in the heel to toe test. There was no evidence of incoordination in any of the extremities. Motor power was well preserved throughout. The tendon reflexes were equally active in the arms

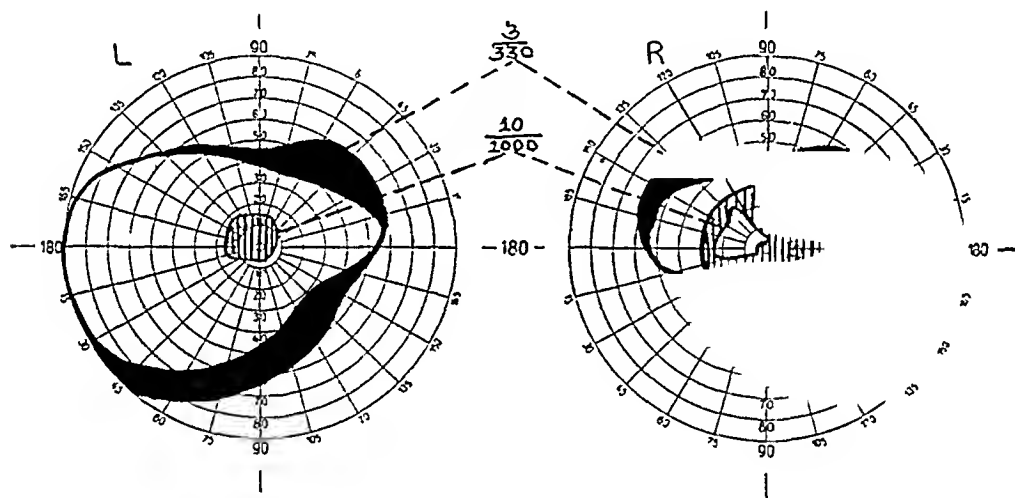


Fig 1 (case 1)—Visual fields, showing central scotoma in the left eye and temporal hemianopsia with nasal pericentral ring scotoma in the right eye

and legs. The abdominal reflexes were equally active on the two sides. No pathologic reflexes were noted. Pain, position and vibration sensations were intact throughout.

The fundi showed pallor of both optic disks. Visual acuity was 6/30 in the right eye and 1/60 in the left eye. There were a central scotoma in the left eye and a combined central and peripheral visual field defect in the right eye (fig 1). The pupils were equal and regular and reacted well to light and in accommodation. The extraocular movements were normal. The corneal reflexes were equally active. No facial, palatal or lingual weaknesses were observed.

Laboratory Data—A blood count revealed 78 per cent hemoglobin, 4,110,000 red cells, 7,900 white cells and a color index of 0.95 with 76 per cent neutrophils, 22 per cent lymphocytes and 2 per cent monocytes. The urine was normal. The serologic reactions of the blood were negative for evidence of syphilis. The spinal fluid was clear and colorless and was under an initial pressure of 190 mm, it contained 1 cell per cubic millimeter, the serologic reactions were negative.

and the colloidal gold curve was normal. A roentgenogram of the skull showed slight demineralization of the dorsum sellae but was otherwise normal.

Course—After a short period of observation, the patient was discharged from the hospital unimproved. Visual impairment progressed gradually, and two years later, in 1941, severe headaches appeared. The headaches recurred at increasingly frequent intervals and were unrelieved by acetylsalicylic acid. Six months later the headaches were associated with projectile vomiting. In January 1942, three years after the onset of symptoms, a mental disorder became evident in conjunction with the development of an abscess of the breast. On admission to the Germantown Hospital, on Feb. 9, 1942, the patient was found to be exhausted and moderately anemic. She was somnolent and emotionally labile. The significant neurologic observations were amaurosis, a dirty gray pallor of the optic disks and dilated pupils, which did not respond to light but reacted in accommodation. An electroencephalogram showed abnormal slow waves throughout both hemispheres. A roentgenogram of the skull was normal. A ventriculogram showed changes indicative of a suprasellar neoplasm. Craniotomy revealed a suprasellar meningioma, originating in front of the optic chiasm but extending back over the sphenoid ridge into the right middle fossa. Three days after a second craniotomy, for the purpose of completing removal of the tumor, the patient died, on April 19.

Comment—This case illustrates clearly the problems under discussion. The onset of the visual loss was sudden and was so rapidly progressive that almost all vision was lost in the course of a month. The optic disks were pale at the time of the patient's first admission, and the visual fields revealed scotomatous defects. The subsequent course was characterized by further loss of vision, the development of headache and more pronounced atrophy of the optic nerve.

The symptoms at the time of onset were much more typical of retrobulbar neuritis than of a suprasellar tumor, as evidenced by the sudden loss of visual acuity and the scotomas. The occurrence of partial remission of impaired vision in this case following intensive vitamin therapy was another feature which could easily be misinterpreted as favoring the diagnosis of neuritis. Only with the appearance of persistent headache was the diagnosis of tumor seriously regarded and eventually established.

CASE 2—A girl aged 16, admitted on Jan. 18, 1940, with history of headaches for three years and impairment of vision for four months, bilateral atrophy of optic nerve, with combined central and peripheral field defects in both eyes, death on Feb. 10, 1940, following operation, verified diagnosis of suprasellar meningioma.

History—B. D., a girl aged 16 years, was admitted to the neurologic service of the Jefferson Medical College Hospital on Jan. 18, 1940. The family history was noncontributory. The past medical history revealed that the patient had been in good health except for childhood diseases.

The onset of the present illness occurred three years previously, with moderately intense headaches in the occipital region, lasting one or two hours and recurring at weekly intervals. At that time, the patient had impairment of distant vision, but near vision was good. After refraction vision was completely satisfactory.

The headaches also became less frequent and less intense but continued to recur at intervals of one or two months. Episodes of vertigo first developed in September 1939, at which time it was noticed that the patient was holding objects closer to her eyes while reading. About one month later the patient awoke during the night with vomiting and an excruciating headache, which persisted for one or two days. A similar episode of headache and vomiting occurred two weeks later. Headaches and vertigo continued to recur frequently thereafter. One month after this she showed evidence of impairment of memory, which was noticed by members of her family, and still another month later gradually increasing impairment of vision developed. Her condition remained unchanged until Jan 2, 1940, when she awoke in the morning to discover that her vision had failed to such a degree that she was unable to read. Several hours later a severe occipital headache developed, persisted for a short time and recurred at irregular intervals throughout the day. During the next day, vision remained blurred and the headache returned. On one occasion that day, when she was assuming the erect position, vertigo appeared and persisted for five minutes. The headaches continued to recur daily, and the episodes of vertigo reappeared occasionally. At times the patient noticed an aching sensation in her eyes. Impairment of memory and concentration were marked a few days before her admission to the hospital.

Examination—Physical examination revealed fairly good development. The thyroid was slightly enlarged. The nose, throat and sinuses showed no evidence of infection. The lungs and abdomen were grossly normal. The heart was slightly enlarged, and there was a presystolic murmur over the apex. The blood pressure was 114/82.

Neurologic examination revealed unsteadiness in standing on either leg alone and in the heel to toe test. There was no evidence of incoordination in the finger to nose or the heel to knee test. Motor power was well preserved throughout. There was generalized tendon hyporeflexia. The abdominal reflexes were diminished and exhaustible. No pathologic plantar reflexes were noted. Pain, position and vibration senses were intact throughout.

The sense of smell was well preserved. The right fundus showed slight temporal pallor of the optic disk, with the lamina cribrosa visible in a broad, deep cup. The left fundus showed pronounced silvery gray pallor of the entire optic disk with slight edema of the nasal margin, and the lamina cribrosa was not visible in the temporal portion of the cup. There was some fulness of the retinal veins bilaterally, the retinal arteries appeared normal. Visual acuity was 5/200 in each eye. Examination of the visual fields showed peripheral and central defects in both eyes (fig 2). The pupils were large, equal and regular and reacted well to light and in accommodation. Extraocular movements were normal. No facial, palatal or lingual weaknesses were observed.

Laboratory Data—The urine was normal. The blood count showed 72 per cent hemoglobin, and 4,000,000 red cells, 8,500 white cells, a color index of 0.88, with 79 per cent neutrophils, 20 per cent lymphocytes and 1 per cent monocytes. The serologic reactions of the blood were negative for evidence of syphilis. The blood contained 29 mg of nonprotein nitrogen, 12.34 mg of urea nitrogen and 90 mg of sugar, per hundred cubic centimeters. Urea clearance was 100 per cent, average normal volume of urine per minute. The spinal fluid was clear and colorless, the initial pressure was 150 mm, the fluid contained less than 1 cell per cubic millimeter, the Wassermann reaction was negative, and the total protein measured 54 mg per hundred cubic centimeters. The electrocardiogram showed

a left axis deviation but was otherwise normal. The Barany test revealed abnormal reactions, which were interpreted as being the result of "a lesion in the region of the decussation of the superior cerebellar peduncles." A roentgenogram of the skull was normal. A roentgenogram of the sinuses disclosed evidence of chronic hyperplastic ethmoiditis bilaterally and right frontal sinusitis.

Course—After her admission to the hospital, the patient did not complain of headaches, but the pronounced impairment of vision persisted. Repeated

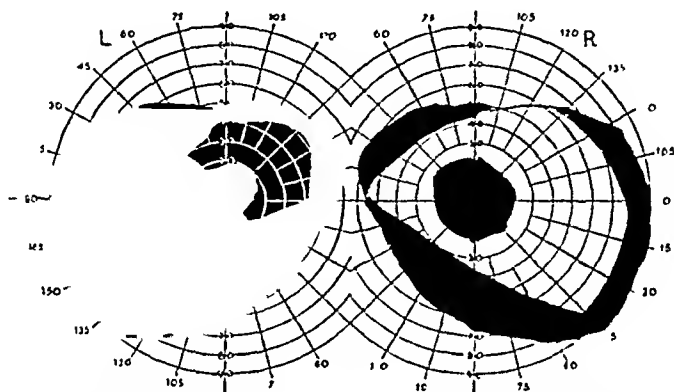


Fig 2 (case 2)—Visual fields (10 mm test object, distance, 330 mm, daylight), showing central scotoma merging inferiorly with temporal hemianopsia in the left eye and central scotoma in the right eye. Vision was limited to counting fingers at 6 inches (15 cm) in each eye (eccentric).

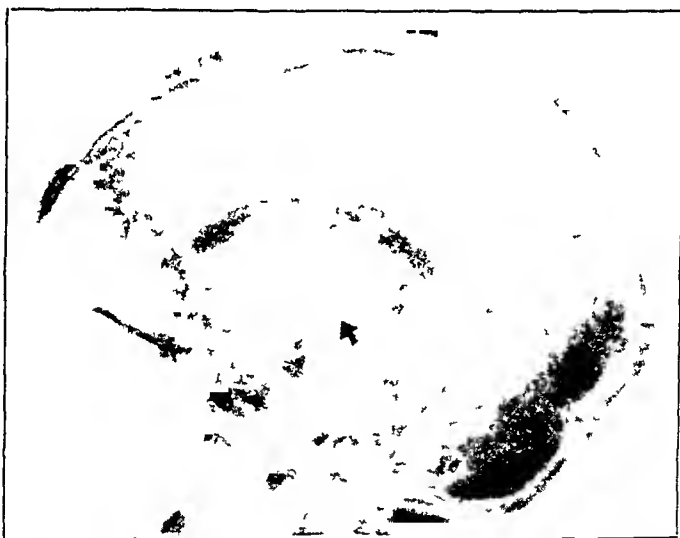


Fig 3 (case 2)—Pneumoencephalogram, showing obliteration of cisterna chiasmatis and encroachment on the floor of the third ventricle.

examination of the fundi during the first week after her admission disclosed slightly increasing edema of the nasal margin of the left optic disk, with extension to the upper and lower margins, but without measurable elevation. The appearance of the fundi was unchanged during the second week.

Pneumoencephalographic examination (fig 3) was performed, and the report follows: "Obliteration of the cisterna chiasmatis was seen in the lateral view

In this region there was a sharply demarcated shadow, suggestive of a space-taking lesion in the suprasellar region. The third ventricle was encroached on, and there may have been some elevation of the right lateral ventricle, as seen in the sagittal view."

Reexamination of the visual fields one week after this showed enlargement and alterations in outline of the defects bilaterally (fig 4)

A right frontal craniotomy was performed on February 7, and the report follows: "The frontal lobe was retracted, and a mulberry-like, pink mass was found near the midline. The right optic nerve was seen to be widely stretched over the neoplasm, which protruded laterally beneath the nerve. The major portion of this mass appeared in the anterior fossa medial to the right optic nerve, although it extended caudal to the medial end of the right sphenoid ridge."

After operation, the patient remained comatose, with progressive elevation of temperature to a level of 108 F at the time of her death, on February 10.

Autopsy—A moderate extravasation of coagulated blood was observed beneath the bone flap in the right frontal and parietal regions. The tip of the right

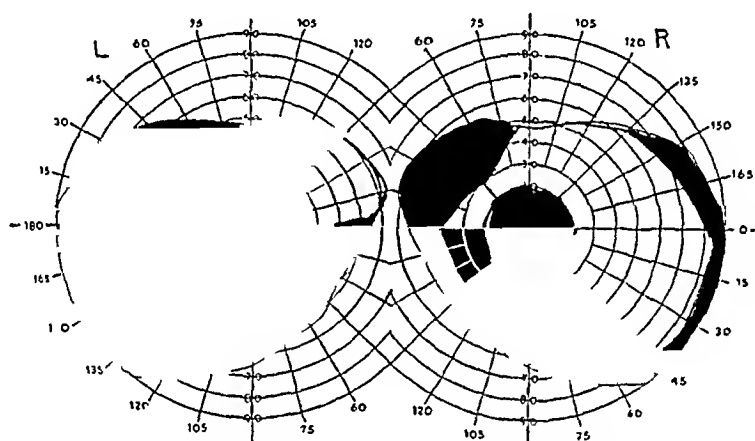


Fig 4 (case 2)—Fields (10 mm test object, distance, 330 mm, daylight) taken two weeks after those shown in figure 2, showing expansion of defect, with vision limited to the superior nasal quadrant in the left eye and merging of central scotoma inferiorly with peripheral indentation in the right eye.

frontal lobe was slightly macerated, and the brain generally was edematous. The area of the chiasmatic cistern was occupied by a firm, fleshy, walnut-shaped tumor (fig 5), which measured 2.5 by 3.5 by 3 cm. The posterior limit of the tumor was in the optic chiasm, and its anterior limit extended just proximal to an imaginary line joining the tips of the temporal poles. The surface of the tumor had been macerated (after operation). The olfactory bulbs and tracts could not be identified. The interpeduncular fossa was obliterated with hemorrhage. Microscopic examination revealed a meningioma.

Comment—The problem in this case was somewhat simpler in some respects than that in the first case, but the diagnosis of a suprasellar tumor was still difficult in the absence of typical hemianoptic field defects. The early appearance of headache and its persistence aroused suspicions that a cerebral tumor was present, and the occurrence of atrophy of the optic nerve appeared to confirm the suspicion, but the

presence of scotomatous field deformities was unusual. In this instance, the problem was not complicated by sudden visual loss, but visual acuity was low (5/200 in each eye) and seemed to be far below the acuity to be expected from the appearance of the fundi. On the whole, the possibility of tumor was so definite, largely because of the headache, and despite the features of retrobulbar neuritis, that a pneumoencephalographic examination was performed, revealing a suprasellar tumor. Another noteworthy feature in this case is the age of 16 years, which is consider-

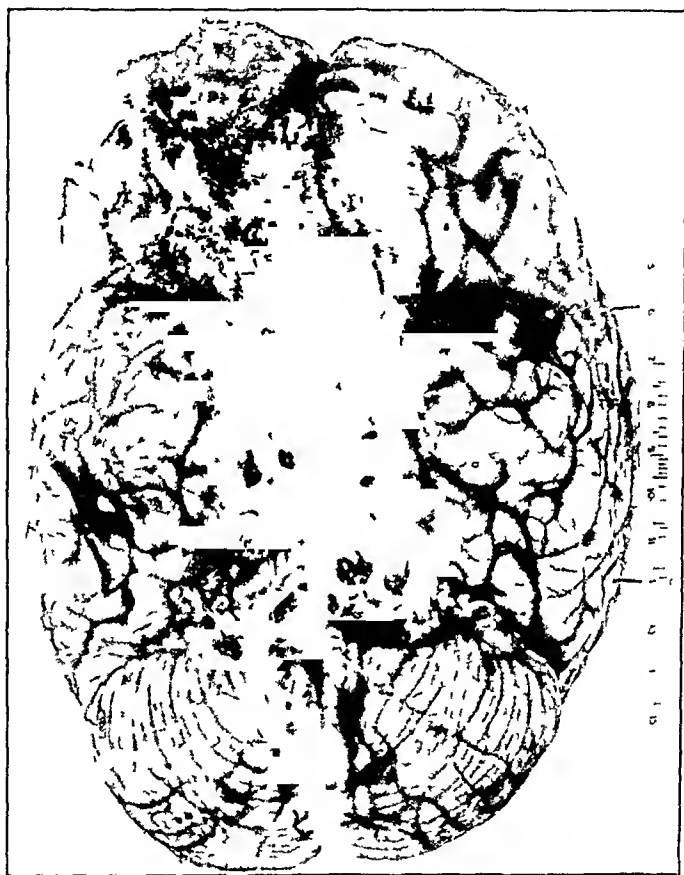


Fig 5 (case 2) —Basilar view of brain, with suprasellar meningioma occupying cisterna chiasmatis

ably below the youngest age recorded previously, that of 27 years, reported by Cushing and Eisenhardt¹ in their series of cases of suprasellar meningioma.

CASE 3—A woman aged 31, admitted on April 24, 1940, with history of rapidly failing vision of right eye for four months and of left eye for one month, anosmia on left side, bilateral optic nerve atrophy, with papilledema in right eye and

1 Cushing, H., and Eisenhardt, L. *Meningiomas*, Springfield, Ill., Charles C Thomas, Publisher, 1938

combined central and peripheral field defects of both eyes, progression of visual impairment prior to operation, on May 2, 1940 Patient discharged with verified diagnosis of suprasellar meningioma

History—E H, a woman aged 31, was first observed at the Wills Hospital on the service of Dr W J Harrison and was subsequently admitted to the neurologic service of the Jefferson Medical College Hospital, on April 24, 1940 The family history was noncontributory The past medical history revealed that the patient had been in good health except for minor diseases of childhood She was a clerk by occupation and had no history of exposure to any known exogenous poisons

The onset of the present illness occurred four months prior to her admission to the hospital with blurring of vision and a sensation of mist and a spot before the right eye Within a short time the patient was unable to read with this eye At that time she noticed mild frontal headaches, which appeared usually in the morning, but after treatment for supposed sinus infection the headaches completely disappeared The impaired vision of the right eye became progressively worse Within the month preceding her admission, impairment of vision of the left eye appeared and progressed rapidly, so that the patient was unable to read with either eye Double vision was noticed for a short period prior to hospitalization There was no history of impairment of memory or alteration of personality

Examination—Physical examination revealed a relatively slender woman, of small stature Examination of the nose and throat showed a thickened, hyperplastic mucous membrane in both ethmoid areas The tonsils were small and embedded The heart, lungs and abdomen were grossly normal The blood pressure was 110 systolic and 70 diastolic

Neurologic examination revealed normal station and gait There was no evidence of incoordination in any of the extremities Motor power was well preserved throughout The tendon reflexes were equally active in the arms The patellar and achilles reflexes were hyperactive bilaterally, being possibly more pronounced in the right leg than in the left No pathologic plantar reflexes were noted Pain, position and vibration senses were intact throughout

There was anosmia on the left, with odors perceived but not identified on the right The right fundus showed papilledema of 2 D at the nasal margin of the optic disk, with the swelling diminishing over the remainder of the disk and a small area free of edema near the inferior temporal margin, in the area which was free of edema a small part of the lamina cribrosa was visible and seemed pale, while the swollen portion of the disk was congested The left fundus showed definite pallor of the optic disk, most pronounced temporally, with the margins of the disk well outlined and considerable lamina cribrosa visible in the broad, deep cup The retinal arteries and veins bilaterally were somewhat tortuous, but there was no venous engorgement The macular area was normal bilaterally Visual acuity was 1/60 in the right eye and was limited to counting fingers at 18 inches (45 cm) in the left eye Examination of the visual fields on April 18, 1940 at the Wills Hospital showed peripheral and central defects in both eyes (fig 6) The pupils were dilated and not quite round, with the right pupil reacting sluggishly to light directly and not reacting consensually, the left pupil failed to react to light directly but reacted consensually There was slight paresis of the external rectus muscle bilaterally, with the extraocular movements otherwise normal The corneal reflexes were equally active on the two sides There was no weakness of the face, palate or tongue

Laboratory Data—The urine was normal. The blood count showed 75 per cent hemoglobin, 4,500,000 red cells, 4,300 white cells and a color index of 0.83, with 62 per cent neutrophils, 35 per cent lymphocytes and 3 per cent monocytes. The blood contained 29 mg of nonprotein nitrogen and 114 mg of sugar, per hundred cubic centimeters. The serologic reactions of the blood were negative for evidence of syphilis. The spinal fluid was blood tinged, the initial pressure was 55 mm, the Wassermann reaction was negative, and the total protein measured 18 mg per hundred cubic centimeters. The electrocardiogram was within normal limits.

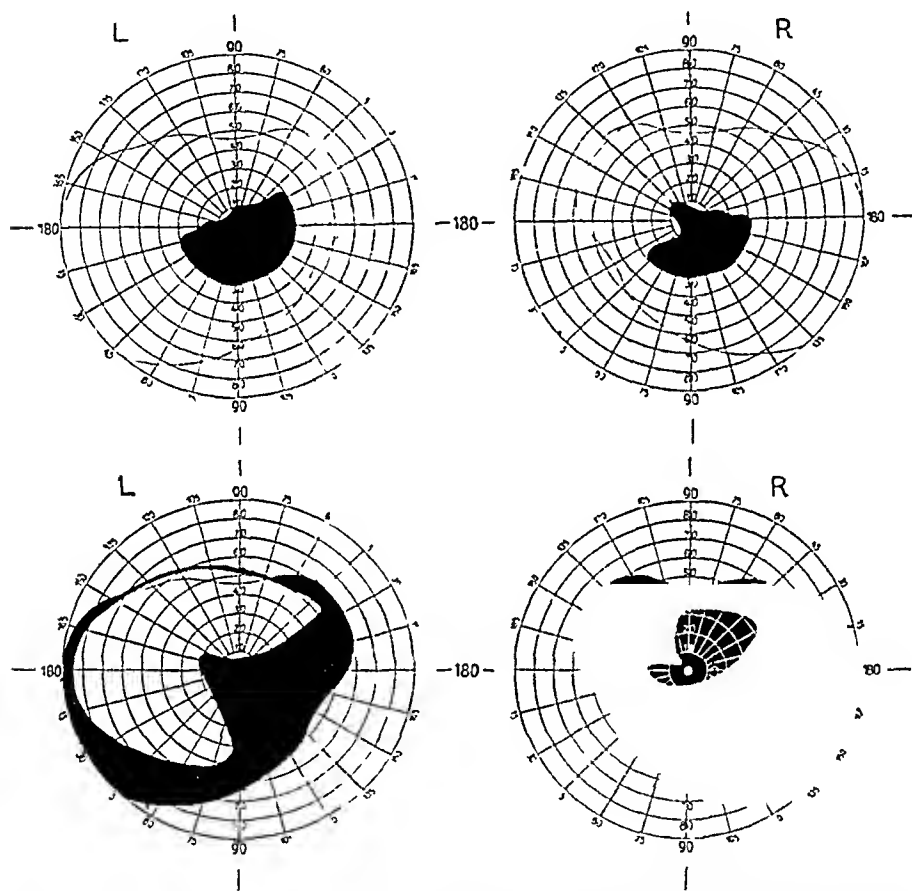


Fig 6 (case 3)—Visual fields, showing obliquely inferior altitudinal central scotoma bilaterally with peripheral constriction, which is nasal on the left and more uniform on the right.

A roentgenogram of the skull showed haziness of all the sinuses, with evidence of destructive changes involving the anterior portions of the sphenoid bone. The destructive changes were more advanced on the right side. There was no evidence of increased intracranial pressure. The sella turcica was normal in size and shape. The left optic foramen was small and distorted in outline, while the right optic foramen was well visualized.

Course—Vision continued to become progressively worse after the patient's admission to the hospital. Reexamination of the visual fields eleven days after the original study revealed considerable extension of the field defects (fig 7).

Craniotomy was performed on May 2, 1940, and the report follows: "After incision of the dura transfrontally and retraction of the right frontal pole, an

encapsulated neoplasm was discovered lying directly in the midline. The neoplasm was at least as large as a lemon and extended caudally as far as could be visualized, while medially it extended beneath the free edge of the falx. The roof of the right orbit appeared distorted and more prominent than normal. After incision of the capsule, tumor tissue, having a honeycombed appearance, was removed and found to be rather vascular. The neoplasm appeared to extend directly into the sphenoid sinus and into the cribriform plate. The optic nerves and anterior cerebral arteries could not be visualized and were believed to be embedded within the tumor. No attempt was made to remove the neoplasm from a wide area." After operation the patient reacted favorably, but vision remained limited to light perception in the right eye at the time of discharge, on May 24, 1940.

Microscopic examination of tumor fragments removed at operation revealed a meningioma.

Comment—The course of the illness in this instance was rapid, with headaches and development of visual loss over a period of four months. The loss of vision was more prominent than headache and had pro-

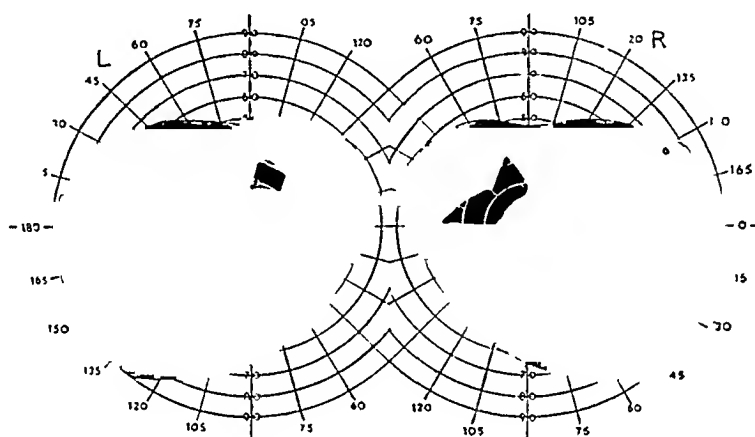


Fig 7 (case 3)—Fields taken with 15 mm test object at distance of 330 mm, with daylight illumination, eleven days after those in figure 6, showing expansion of defects bilaterally, with remnant of vision limited to the upper nasal quadrant bilaterally (left eye, perception of hand movements, right eye, counting fingers at 9 inches [22 cm]).

gressed to such a degree for three months in the right eye and for one month in the left eye that the visual acuity at the time of examination was 1/60 in the right eye and was limited to perception of form at 18 inches (46 cm) in the left eye. Despite rapid visual loss and presence of scotomas, the possibility of tumor was regarded as good, though it is doubtful whether the diagnosis could have been established with certainty without pneumoencephalographic studies had it not been for the destructive changes in the region of the sella turcica. It was this lesion which established the diagnosis definitely in the present case. It is interesting to note that the headache disappeared completely with treatment of the sinuses. It is also noteworthy that the penultimate stage of visual impairment was reached in the superior nasal quadrants.

This agrees with the observations of Traquair² and de Schweinitz,³ who described the penultimate stage as usually consisting of vision limited to the superior nasal quadrants. On the other hand, Cushing and Walker⁴ described the penultimate stage as usually consisting of vision limited to the inferior nasal quadrants.

CASE 4—A woman aged 23, admitted Aug 19, 1942, with history of headaches and increasing visual impairment of left eye for three months, followed by failing vision of right eye for one month, optic nerve atrophy in the left eye with merged central and inferior altitudinal defects in left eye and a central scotoma for color in right eye, progression of visual impairment. Verified diagnosis of suprasellar meningioma.

History—C V, a woman aged 23, was admitted to the Jefferson Medical College Hospital on Aug 19, 1942. The family history was noncontributory. The past medical history disclosed that the patient had been in good health except for minor diseases of childhood.

The onset of the present illness occurred three months prior to her admission with visual impairment of the left eye associated with dull pain in the left supra-orbital region. There were also frequent headaches in the frontal region and occasional headaches in the left temporal area. The pain in the left supraorbital region subsided within three weeks, but the more diffuse headaches persisted. Impairment of vision in the left eye became progressively worse, and within the month before hospitalization gradually increasing visual impairment of the right eye was also noticed.

Physical Examination—The patient was moderately obese, her heart, lungs and abdomen were grossly normal. The blood pressure was 118 systolic and 70 diastolic. Survey of the nose and throat showed a slightly inflamed and thickened nasal mucosa but no definite evidence of sinusitis.

Neurologic examination revealed no disturbance of station or gait. There was no evidence of ataxia or dyssynergia. The motor power was well preserved throughout. The tendon reflexes were equally active in the arms and legs on the two sides. No pathologic reflexes were elicited. Pain, position and vibration senses were unimpaired.

The fundi showed slight pallor of the left optic disk, more evident on the nasal side. Examination of the visual fields showed an inferior altitudinal defect, merging with a central scotoma on the left and a central scotoma for color on the right (fig 8). The pupils were equally dilated and regular in outline and reacted well to light and in accommodation, but the reaction to light was not normally sustained. The extraocular movements were normal. The corneal reflexes were equally active on the two sides. There were no weaknesses of the face, palate or tongue.

Laboratory Data—The urine was normal. The blood count revealed 78 per cent hemoglobin, 4,100,000 red cells, 8,200 white cells and a color index of 0.95.

2 Traquair, H. M. Bitemporal Hemipia. The Later Stages and the Special Features of the Scotoma, *Brit J Ophth* **1** 216, 281 and 377, 1917.

3 de Schweinitz, G. E. Visual Phenomena in Pituitary Body Disease, *Tr Coll Physicians*, Philadelphia **37** 98, 1915.

4 Cushing, H., and Walker, C. B. Distortions of the Visual Fields in Cases of Brain Tumor. Chiasmal Lesions, with Especial Reference to Bitemporal Hemianopsia, *Brain* **37** 341, 1915.

The serologic reactions of the blood were negative for evidence of syphilis. The spinal fluid was clear and colorless. The pressure was normal, there was less than 1 cell per cubic millimeter, the Wassermann reaction was negative, and the colloidal gold curve was normal.

Course—Vision became progressively worse, and reexamination of the visual fields three weeks after the original study revealed extension of the field defects (fig 9). An encephalogram was interpreted as inconclusive because of complete absence of filling of the ventricular system, the subarachnoid pathways were

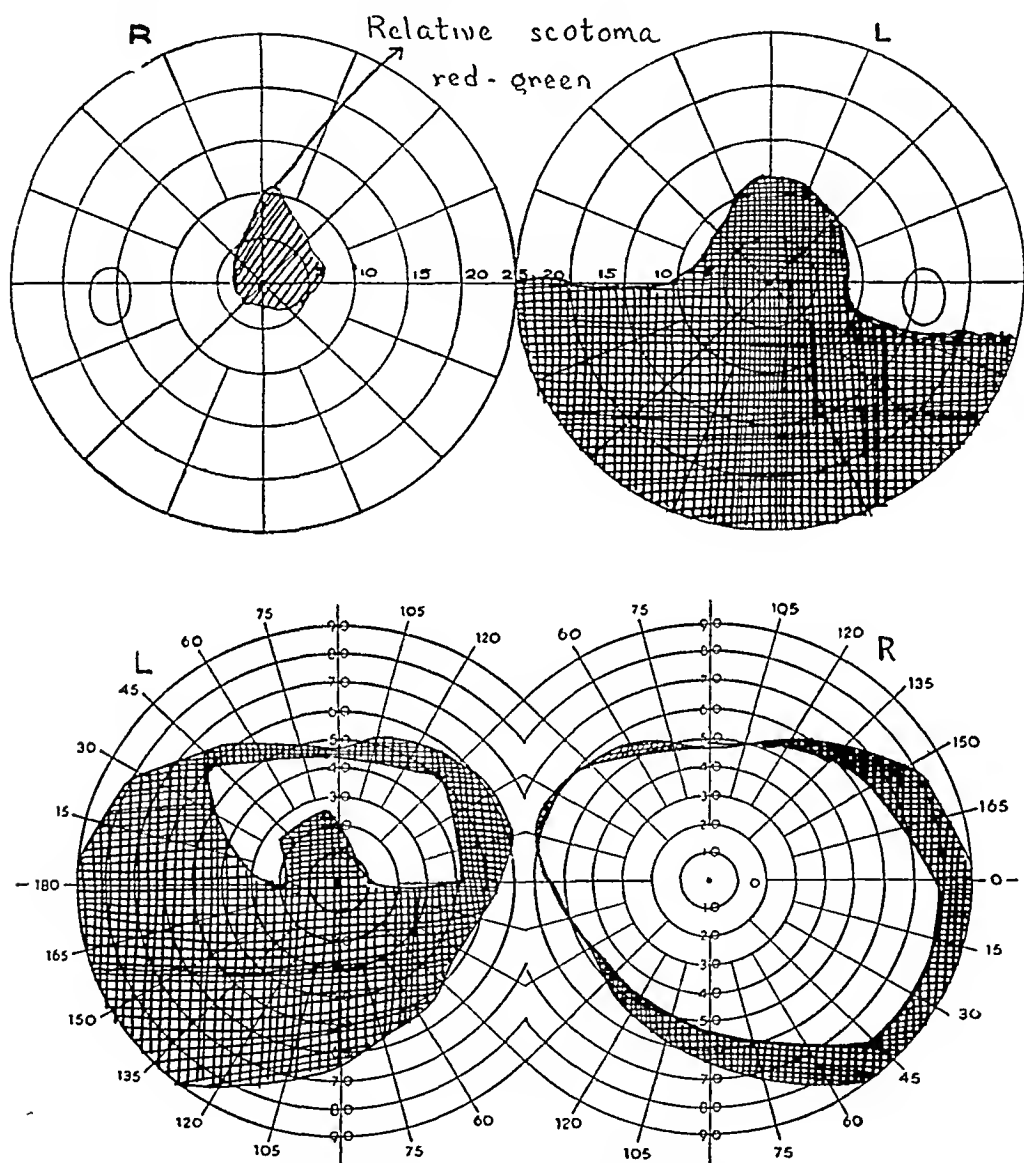


Fig 8 (case 4)—Visual fields (15 mm white test object for left eye, 5 mm test object for right eye, distance, 330 mm, daylight illumination), showing central scotoma merging with inferior altitudinal defect in the left eye and relative central scotoma in the right eye. Vision right eye, 10/200 without glasses and 20/200 with glasses, left eye, perception of hand movements.

described as having "a fairly normal appearance." The patient was discharged on Sept 17, 1942, with her condition unimproved. Subsequent information, obtained from another hospital, disclosed that a suprasellar meningioma had been found at operation.

Comment—Here too, the course was rapid over a period of three months, and headaches and visual loss were the outstanding symptoms. Optic nerve atrophy was not prominent, and the field defects were not of a hemianoptic type. Noteworthy in this case was the presence of an inferior altitudinopia in the left eye. Though tumor was suspected, a

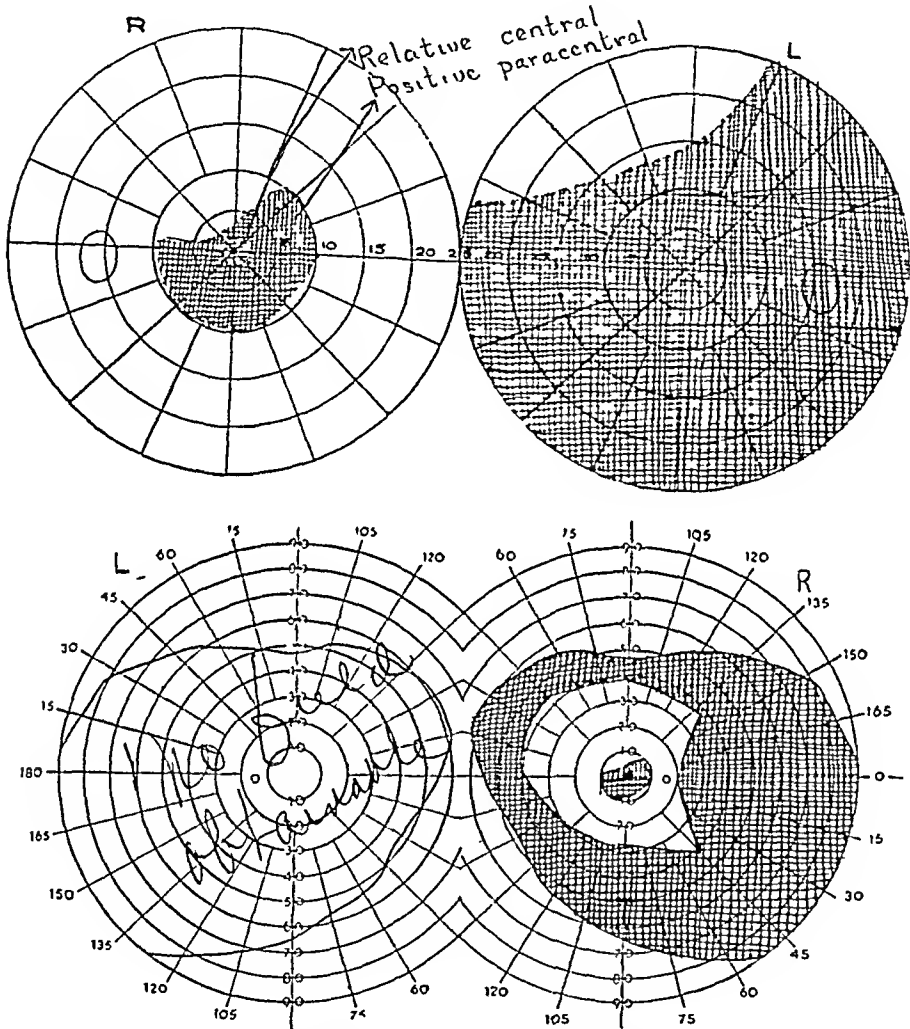


Fig 9 (case 4)—Fields taken with 5 mm test object at 330 mm, daylight illumination, three weeks after those in figure 8, showing expansion of defect to near obliteration of vision on the left (perception of hand movements) and definite central scotoma with peripheral constriction on the right. Vision in the right eye was 5/200 with and without glasses.

pneumoencephalogram gave inconclusive evidence, and the patient was discharged, only to have a suprasellar meningioma revealed at operation in another hospital. The rapid expansion of field defects is significant and indicates the need for speed in diagnosis and in neurosurgical intervention whenever central scotomas become manifest.

GENERAL COMMENT

The meningiomas in the suprasellar region have been described by Cushing⁵ as arising from the meninges overlying the circumsellar venous sinuses. The need of more accurate localization of these meningiomas as to their site of origin from the tuberculum sellae was later appreciated by Cushing and Eisenhardt,⁶ who also described in detail the common clinical features of these tumors. An early clinicopathologic report of a suprasellar meningioma was made by Stewart,⁷ and it illustrates the clinical course of such a lesion prior to the advent of neurosurgical intervention. Dandy⁸ and Cushing⁵ both reported in 1922 their results in exploring the region of the optic chiasm. Subsequently, the operative accessibility of the suprasellar meningioma was emphasized by Holmes and Sargent⁹ and by Cushing¹⁰. At the stage at which this tumor is more easily removable, it does not deform the sella turcica and does not cause symptoms of endocrine dysfunction. Consequently, the importance of correctly interpreting the fundus and, more especially, the alterations in the visual fields when these symptoms first appear in such cases is obvious.

As a basis for a clearer appreciation of the varied types of defects of the visual fields which may be caused by suprasellar meningiomas, a brief survey of the regional anatomy would not be amiss. Grossly, the optic nerve at the apex of the orbit passes through the optic canal, in which it lies above the ophthalmic artery. Intracranially, the optic nerves cross the internal carotid arteries dorsally before reaching the optic chiasm. At one time the optic chiasm was thought to have a rather constant position in relation to the base of the skull in the region of the chiasmatic sulcus. However, Schaeffer¹¹ has conclusively demonstrated that in the majority of instances the chiasm is in the neighbor-

5 Cushing, H. The Meningiomas (Dural Endotheliomas). Their Source and Favored Seats of Origin, *Brain* **45** 282, 1922.

6 Cushing, H., and Eisenhardt, L. Meningiomas Arising from the Tuberculum Sellae, *Arch Ophth* **1** 1 (Jan.), 168 (Feb.) 1929.

7 Stewart, J. The Symptomatology of Tumors Involving the Hypophysis, *Tr A Am Physicians* **14** 282, 1899.

8 Dandy, W. E. Prechiasmal Intracranial Tumors of the Optic Nerves, *Am J Ophth* **5** 169, 1922.

9 Holmes, G., and Sargent, P. Suprasellar Endotheliomata, *Brain* **50** 518, 1927.

10 Cushing, H. The Chiasmal Syndrome of Primary Optic Atrophy and Bitemporal Field Defects in Adults with a Normal Sella Turcica, *Arch Ophth* **3** 505 (May), 704 (June) 1930.

11 Schaeffer, J. P. Some Points in the Regional Anatomy of the Optic Pathway, with Especial Reference to Tumors of the Hypophysis Cerebri and Resulting Ocular Changes, *Anat Rec* **28** 243, 1924.

hood of the diaphragma sellae, a site considerably posterior to the sulcus chiasmatis

We are concerned in this paper chiefly with the defects of the visual fields which may result from the destructive action of a suprasellar meningioma on the primary visual pathways. Although it might be expected that such a lesion would produce constant and predictable alterations in the visual fields, owing to compression of the chiasm, it is not an uncommon experience to find that the expected changes in the visual fields, namely, symmetric bitemporal hemianoptic defects, are absent. However, the anatomic fact previously mentioned, that the optic chiasm is most often located in the neighborhood of the diaphragma sellae, may be correlated with the fact that the suprasellar meningiomas originate in the region of the tuberculum sellae, resulting in the inescapable conclusion that many, if not the majority of, such neoplasms will initially affect the prechiasmal portions of the visual pathway rather than the chiasm. This is sufficient to explain the tendency toward asymmetry of the temporal field defects and the absence of homonymous hemianoptic field defects, as well as the occurrence in some instances of altitudinal field defects. These observations are apparent in our cases and have been pointed out previously by Cushing and Eisenhardt⁶

Our cases demonstrate in a striking manner the somewhat surprising and unexpected clinical observation that suprasellar meningiomas are in some instances associated with a syndrome which includes scotomatous field defects. These scotomas sooner or later join with a peripheral field defect to produce an expanding sector defect which ultimately results in blindness. Scotomatous field defects have been said to occur in about 15 per cent of cases of tumors of the pituitary gland,¹² have been described by Lillie¹³ in cases of chiasmal arachnoiditis and are included as a feature of the Foster Kennedy syndrome¹⁴. However, a survey of the literature discloses that the relatively early appearance of central scotomatous field defects in cases of suprasellar meningioma has not been sufficiently emphasized. The central scotoma in such cases presents a difficult problem in diagnosis, often being attributed to retrobulbar neuritis or to multiple sclerosis rather than being considered as a possible sign of tumor in the suprasellar region. Of help in early differential diagnosis may be the outline of an incompletely developed scotoma in the central field. In addition to the out-

12 Alpers, B. J. *Diagnosis and Treatment of Pituitary Tumors*, M. Clin. North America **26** 1679, 1942.

13 Lillie, W. I. *Prechiasmal Syndrome Produced by Chronic Local Arachnoiditis*, Arch. Ophth. **24** 940 (Nov.) 1940.

14 Kennedy, F. *Retrobulbar Neuritis as an Exact Diagnostic Sign of Certain Tumors and Abscesses in the Frontal Lobes*, Am. J. M. Sc. **141** 355, 1911.

line of the central field defect, which at times may be fully developed when the patient is first seen, an important characteristic of such fields is the peripheral indentation which is almost always present and which sooner or later merges with the central defect to produce an expanding sector defect in the visual field

The relationship between the location of lesions involving the primary visual pathway and the type of central scotoma was reviewed by Walsh and Ford¹⁵ It was indicated by these authors that a unilateral, roughly circular, pericentral scotoma results from involvement of macular or papillomacular bundles Hemianoptic scotomas, which are often associated with a contralateral peripheral field defect, were described by Traquair¹⁶ as being a result of lesions at the junction of the optic nerve and the optic chiasm Lesions of the posterior portion of the chiasm are said to cause bitemporal central and peripheral field defects According to Walsh and Ford,¹⁵ lesions at the posterior angle of the chiasm result in homonymous field defects, which centrally may include a contralateral temporal scotoma, either alone or combined with a homolateral pericentral scotoma

Consideration previously given to the appearance of central scotomatous field defects as a manifestation of lesions in the region of the optic chiasm has been largely in connection with their occurrence as a result of tumors of the pituitary body Attention was first directed to the existence of an expanding paracentral defect in cases of such tumors by Foerster¹⁷ In his comprehensive discussion of the ocular aspects of disorders of the pituitary body, de Schweinitz¹⁸ reviewed the various hypotheses which have been offered to explain the pathogenesis of such central field defects These explanations have variously emphasized the factors of pressure, traction,¹⁹ individual variations in the composition of the chiasm²⁰ and the selective affinity of toxins for the macular fibers²¹ Traquair² expressed the belief that the

15 Walsh, F B, and Ford, F R Central Scotomas, *Arch Ophth* **24** 500 (Sept) 1940

16 Traquair, H M An Introduction to Clinical Perimetry, St Louis, C V Mosby Company, 1927

17 Foerster Beziehungen der Krankheiten des Nervensystems zum Sehorgan, in Graefe, A, and Saemisch, T Handbuch der gesamten Augenheilkunde, Leipzig, W Engelmann, 1877, vol 7, p 116

18 de Schweinitz, G E Concerning Certain Ocular Aspects of Pituitary Body Disorders, Mainly Exclusive of the Usual Central and Peripheral Hemianopic Field Defects, *Tr Ophth Soc U Kingdom* **43** 12, 1923

19 Fisher, J H, in Discussion on Disease of the Pituitary Body, *Proc Roy Soc Med* **6** 53, 1913

20 de Schweinitz, G E, and Carpenter, J T Ocular Symptoms of Lesions of the Chiasma, *J A M A* **44** 81 (Jan 14) 1905

21 Fuchs, E, in discussion on Benson Case of Acromegaly, *Brit M J* **2** 949, 1895

acuteness of pressure with impairment of the vascular supply to the macular fibers, rather than the site of such pressure on the primary visual pathways is responsible for the occurrence of central scotomas. Generally accepted has been the significant and relevant physiologic fact that the macular fibers are relatively more susceptible to pressure and toxic factors than the rest of the visual fibers. This physiologic principle together with the anatomic principle based on the studies of Schaeffer,¹¹ serves as a reasonable basis for understanding the early, and relatively frequent, occurrence of scotomatous field defects in patients having suprasellar meningiomas. Noteworthy in this connection is the conclusion reached by Henderson²² and supported by Jefferson²³ that central scotoma due to adenoma of the pituitary body is indicative of a prefixed optic chiasm with retrochiasmal extension of the tumor. On the other hand, our observations in cases of suprasellar meningiomas, as well as the observations of Wagener and Love²⁴ in cases of tumors of Rathke's pouch, tend to favor the likelihood of a prechiasmal location in such cases.

In the prechiasmal syndrome, as observed in cases of suprasellar meningioma the outstanding symptom is impairment of vision, which in many instances is rapidly progressive. Characteristically, the visual impairment affects the two eyes successively rather than simultaneously, and the time interval is usually measurable in weeks or months rather than in days. In the early stage, optic disks either appear to be within normal limits or show only slight pallor. Later, the optic disks will show more or less pronounced atrophy. The visual field defects are an early and conspicuous clinical feature in the syndrome produced by this tumor. As might be expected, the field defects tend toward the "bizarre" type in which a combination of central and peripheral defects exists. There are wide variations as to the size, shape and position of these field defects. The occurrence of scotomatous field defects centrally is probably more frequent as an initial type of alteration than is commonly recognized, and explains the early rapid failure of vision. The accuracy of the surmise by Holmes and Sargent⁹ in this connection is supported by the observations in our cases. Of similar significance is the case report by Hagedoorn,²⁵ in which a suprasellar meningioma was discovered to be responsible for a bitemporal central field defect. The asymmetry and incomplete

22 Henderson, W. R. The Pituitary Adenomata, *Brit J Surg* **26** 811, 1939.

23 Jefferson, G. Extrasellar Extensions of Pituitary Adenomas, *Proc Roy Soc Med* **33** 433, 1940.

24 Wagener, H. P., and Love, J. G. Fields of Vision in Cases of Tumor of Rathke's Pouch, *Arch Ophth* **29** 873 (June) 1943.

25 Hagedoorn, A. The Chiasmal Syndrome and Retrobulbar Neuritis in Pregnancy, *Am J Ophth* **20** 690, 1937.

character of such central scotomas, emphasized previously by Nettleship,²⁶ as well as their subsequent junction with peripheral temporal or altitudinal field defects, are sufficient in most cases to differentiate suprasellar tumors from retrobulbar neuritis. Peripheral bitemporal field defects unaccompanied with scotomas are the exception, rather than the rule, in cases of suprasellar meningiomas. Asymmetric, altitudinopic field defects are observed in some cases and are pathognomonic of a prechiasmal lesion. In contrast to this, it may be stated that homonymous hemianoptic field defects apparently never occur with suprasellar meningiomas.

We do not believe that it is possible on the basis of the visual field defects alone to differentiate between the various suprasellar lesions which may be responsible for such defects. In addition to meningiomas, other lesions in the suprasellar region that must be considered are adenomas of the pituitary gland, tumors of the hypophyseal duct, gliomas of the optic chiasm, aneurysm and chronic chiasmal arachnoiditis. In their article dealing with visual field defects associated with tumors of the hypophyseal duct, Wagener and Love²⁴ reported the occurrence of unilateral or bilateral central scotoma in 11 of 23 cases and complete amaurosis of one eye in 2 other cases.

Improvements are constantly being made in the differential diagnosis of various lesions which may produce a prechiasmal syndrome. However, vigilance on the part of the neurologist and ophthalmologist is essential in order to avoid the error of attributing scotomatous field defects associated with suprasellar tumors to multiple sclerosis or retrobulbar neuritis. The delays which result from such errors in diagnosis are particularly regrettable in cases of suprasellar meningioma because they so often lead to complete loss of vision or to growth of the tumor to such dimensions that its complete removal becomes extremely hazardous or impossible. Examination of the spinal fluid may be diagnostically valuable if it reveals a positive serologic reaction, an abnormal colloidal gold curve or an elevated total protein content. Cerebral arteriography may be of assistance in cases in which aneurysm is suspected. However, in our opinion, the pneumoencephalographic examination promises to be the most accurate means of establishing or excluding preoperatively the diagnostic possibility of a suprasellar tumor and should be done whenever a prechiasmal syndrome is evident.

SUMMARY AND CONCLUSIONS

The regional anatomy of the prechiasmal and chiasmal portions of the primary visual pathway is such as to make completely uniform

²⁶ Nettleship, E. Central Amblyopia as an Early Symptom in Tumor at the Chiasma, *Tr Ophth Soc U Kingdom* **17** 277, 1897.

alterations in the visual fields resulting from suprasellar lesions practically impossible. Four cases are described which demonstrate the early occurrence of scotomatous field defects in patients with suprasellar meningiomas. Characteristically, the scotomatous field defects in such cases become identifiable as a clue to the existence of a prechiasmal or chiasmal lesion by combining with a peripheral encroachment on the visual field at some point so as to produce an expanding sector defect.

In order to increase further efficiency in establishing an early diagnosis of suprasellar meningioma, we believe that the syndrome of atrophy of the optic nerve with bitemporal visual field defects, as previously emphasized, should be broadened to include the combination of optic nerve atrophy and expanding scotomatous field defects. In the absence of headaches and of deformities of the sella turcica the combination of optic nerve atrophy with either bitemporal or scotomatous field defects is sufficient to warrant routinely the performance of complete examination of the spinal fluid and pneumoencephalography.

Since meningiomas are histologically benign tumors and since the suprasellar location of meningiomas is potentially accessible to the neurosurgeon, an early diagnosis of these tumors is distinctly to be desired.

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HYDROGEN ION CONCENTRATION OF THE AQUEOUS

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THE value of the glass electrode for determination of the hydrogen ion concentration in the vitreous¹ led to its use for similar investigations on the aqueous humor. The studies were indicated in view of the variations in the physiologic values cited in the literature. The differences were often due to the unavoidable errors inherent in the applied methods. Early reports on the p_H of the aqueous lacked reliability, mostly because of the escape of carbon dioxide during the procedure.² After Goldschmidt³ and Baurmann⁴ drew attention to this error, it was usually avoided by methods employed in the examination of similar biologic fluids of moderate buffering capacity.⁵ In general the studies

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1 von Sallmann, L. Hydrogen Ion Concentration of the Vitreous in the Living Eye, *Arch Ophth* **33** 32 (Jan) 1945

2 (a) Foa, C. La reazione dei liquidi dell'organismo col metodo elettrometrico, *Arch di fisiol* **3** 369, 1906. (b) Hertel, E. Ueber die Bestimmung der Wasserstoffionenkonzentration des Kammerwassers, *Arch f Ophth* **105** 421, 1921. (c) Nordenson, J. W. Die Wasserstoffzahl des Kammerwassers bei Feten in verschiedenen Lebensaltern, *Upsala lakaref forhandl* **26** 55, 1921, abstracted, *Zentralbl f d ges Ophth* **7** 515, 1922. (d) Scalinci, N. Ricerche sulla reazione dei liquidi oculari, *Arch di sc biol* **6** 341, 1924. (e) Lehmann, G., and Meesmann, A. Ueber das Bestehen eines Donnangleichgewichtes zwischen Blut und Kammerwasser bzw. Liquor cerebrospinalis, *Arch f d ges Physiol* **205** 210, 1924. (f) Meesmann, A. Ueber die Abhangigkeit des intraokularen Druckes von der Wasserstoffionenkonzentration, *Arch f Augenh* **94** 115, 1924. (g) Schall, E. Das Vorkommen der Nadi Oxydasen in den Gewebszellen des Auges in seinen verschiedenen Entwicklungsstufen, *Arch f Ophth* **115** 666, 1925. (h) Gala, A. Ionenkonzentration des Kammerwassers und Glaskorpers bei normalen und glaukomatosen Augen, *Časop lek česk* **64** 409, 1925, abstracted, *Zentralbl f d ges Ophth* **15** 112, 1926.

3 Goldschmidt, M. Beitrag zur Aetiologie der Cataracta diabetica, *Ber u d deutsch ophth Gesellsch* **45** 191, 1925.

4 Baurmann, M. Die Messung der H-Ionenkonzentration im Kammerwasser, *Ber u d deutsch ophth Gesellsch* **45** 280, 1925, Ueber neue Messungen der H-Ionenkonzentration in menschlichen Kammerwasser, *Arch f Ophth* **118** 36, 1927.

(Footnotes continued on next page)

were conducted along four lines—by the colorimetric method with indicators, by the calculation of the hydrogen ion concentration as a function of the carbon dioxide content, by the calculation of the hydrogen ion concentration on the basis of the accurately determined free carbon dioxide and sodium bicarbonate in the aqueous, and, finally, by direct potentiometric measurement with the hydrogen electrode

The first method of estimating the hydrogen ion concentration, based on the color changes of indicators, is known to be insufficiently accurate, and the error due to the loss of carbon dioxide cannot be fully avoided. In addition, the small amount of test fluid available requires a dilution of the sample, and in a plasmoid aqueous the protein and salt error invalidates the results. Values of the p_H with a range of 6.9 (Schall²⁸) to 7.77 (Lehmann and Meesmann²⁹) were recorded with this technic.

The second method of measuring the p_H by its calculation as a function of an assumed carbon dioxide content of the aqueous was elaborated by Goldschmidt³ and later by Kubik.⁴ They exposed the aspirated sample in a micro-hydrogen-electrode to a carbon dioxide tension of 40 to 50 mm of mercury and estimated the p_H range by means of the Henderson-Hasselbalch formula.

The third method of estimation of the p_H , which was applied by Mawas and Vincent^{5b} and by Kronfeld,^{5a} consisted in its calculation from the accurately determined content of native carbon dioxide and sodium bicarbonate in the same sample of aqueous with the Henderson-Hasselbalch formula. Kronfeld obtained the figures for the calculations with precise methods of gas analysis. His results were in agreement with

5 (a) Salt, P. W. A Study of the Acid-Base Equilibrium of the Ocular Humors, *Biochem J* **24** 596, 1930. (b) Mawas, J., and Vincent, M. Note sur le p_H et la reserve alcaline de l'humeur aqueuse, abstracted, *Ann d'ocul* **162** 620, 1925. (c) Mawas, J. Sur le p_H et la reserve alcaline de l'humeur aqueuse, abstracted, *Skandinav Arch f Physiol* **49** 184, 1926, *Nouvelles recherches sur la concentration ionique et la reserve alcaline de l'humeur aqueuse a l'etat normal et dans les etats glaucomateux*, *Internat Ophth. Cong* **1** 161, 1929. (d) Kronfeld, P. Der Kohlensauregehalt des Kammerwassers, *Arch f Ophth* **118** 606, 1927. (e) Kubik, J. Experimentelle und klinische Untersuchungen uber die Wasserstoffionenkonzentration des Kammerwassers, *Arch f Augenh* **98** 483, 1928. (f) Vincent, M. Action de l'adrenaline en instillation dans le cul-de-sac conjunctival sur les proprietes physicochimiques de l'humeur aqueuse, *Compt rend Soc de biol* **98** 1284, 1928. (g) Tria, E., and de Simone, C. Ricerche chimico-fisiche sui liquidi oculari (acqueo e vitreo), *Arch di sc biol* **17** 274, 1932. (h) Bosa, F. Il p_H nell'acqueo e nel cristallino di animali paratioreoprivi, *Rassegna ital d'ottal* **7** 613, 1938, abstracted, *Zentralbl f d ges Ophth* **43** 162, 1939. (i) Taliercio, A. La cataratta da raggi X, *Ann di ottal e clin ocul* **67** 104, 1939. (j) de Crecchio, A., and Brignola, D. Riserva alcalina del sangue e p_H dell'acqueo nell'acidosi sperimentale, *ibid* **67** 781, 1939. (k) Pignolosa, G. Il p_H dell'umore acqueo nel coniglio nelle affezioni sperimentali di natura tuberculare dell'uvea, *ibid* **69** 307, 1941, abstracted, *Zentralbl f d ges Ophth* **48** 107, 1942.

those obtained by Baurmann,⁴ who first conducted potentiometric measurements of withdrawn samples of the aqueous with the syringe hydrogen electrode. This fourth method was also selected by Mawas and Vincent,⁶ Tria and de Simone,^{5g} Bosa,^{5h} Taliercio,⁵ⁱ Kurose,^{6a} de Crecchio and Brignola^{5j} and Pignolosa.^{5k} Despite the application of the same method on the same experimental animal (rabbit), the p_H values ranged from 7.06 (Tria and de Simone) to 7.61 (Taliercio). It is evident that aqueous fluid, like other solutions with a relatively high content of carbon dioxide, is not well suited to determination of the p_H with the hydrogen electrode. The small quantity of the sample presents another difficulty. Moreover, the protein error of this method excludes its use for plasmoid aqueous.

The glass electrode was scarcely known when most of these reports were published, between 1921 and 1930. In subsequent years it was introduced for determination of the p_H of biologic fluids and tissues and was used extensively in various fields of medical research after the invention of the thermionic amplifier. Nevertheless, a preference for the hydrogen electrode was shown in the studies on the p_H of ocular fluids in the last decade. Except for the use of the glass electrode by Adams and Kerridge in 1930⁷ on the aspirated vitreous fluid and the investigation of this laboratory on the hydrogen ion concentration of the vitreous *in vivo*,¹ there have been no attempts to utilize the advantages of the glass electrode in ophthalmology. These advantages are fully described in the standard text by Dole⁸ and are also reviewed briefly in the study on the p_H of the vitreous.¹

THE GLASS ELECTRODE AND ITS USE

The electrode used in the present study was a modification of the capillary type originally described by MacInnes and Belcher⁹ and improved by Michaelis.¹⁰ It consisted of a straight microcapillary which was sealed into one arm of a U tube (figure). The tube was filled with freshly prepared quinhydrone-hydrochloric acid solution, a platinum wire, which was connected to a Beckman laboratory model potentiometer by means of a shielded lead, was immersed in the solution through the second arm of the U tube. The measuring capillary was made of Corning 015 electrode glass, with a slightly wider and heavier upper

6 Mawas and Vincent^{5b} Mawas^{5c} Vincent^{5f}

6a Kurose, I. *Acta Soc. ophth. jap.* **34** 217, 1930, cited by Crecchio and Brignola^{5j}

7 Adams, D. A., and Kerridge, P. T. The Hydrogen Ion Concentration of the Vitreous, *Brit. J. Ophth.* **14** 397, 1930

8 Dole, M. *The Glass Electrode*, New York, John Wiley & Sons, Inc., 1941

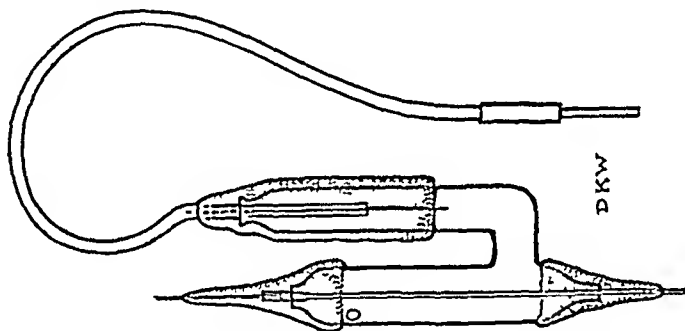
9 MacInnes, D. A., and Belcher, D. A Durable Glass Electrode, *Indust. & Engin. Chem. (Anal. Ed.)* **5** 199, 1933

10 Michaelis, L. Glass Electrode with Galvanometer Reading, *Science* **83** 212, 1936

end, into which was cemented a short, stainless steel, 27 gage needle¹¹ De Khotinsky cement was applied around the base of the needle to form a cone, which gave the needle firm support and permitted its insertion into a rubber sleeve used in the cleaning of the capillary and its standardization with buffers. The cement also covered the free extension of the capillary outside the U tube, to prevent interference by a deviation film, as well as the other arm of the U tube, into which the platinum wire was inserted. Electrodes with a low zero correction, which gave a linear graph with buffers at a p_H of 4, 7 and 8, were selected. The electrodes were calibrated with a buffer solution prior to and after each determination. Readings on the aqueous were considered reliable only when the buffer solution read within 0.02 p_H unit after each experiment. The capillary was thoroughly rinsed with distilled water after each use and with a dilute solution of neutral soap after the determination on a plasmoid aqueous.

TECHNIC OF EXPERIMENTS

The anterior chamber was punctured with the needle, and aqueous was allowed to flow through the capillary until approximately half was drained. After the free end of the capillary was blocked with an agar-potassium chloride disk, the



Micro-glass-electrode used

electrode was withdrawn, the opening of the needle was immediately closed with another agar-potassium chloride disk, and the electrode was then quickly transferred to a shielded constant temperature air chamber¹² in which the calomel half-cell electrode had been placed. Contact was made with the reference electrode by a fluid junction with a saturated solution of potassium chloride. The temperature of the latter was registered on an Anschütz thermometer, and that of the quinhydrone-hydrochloric acid solution in the U tube was measured with a thermocouple. With an appropriate warming of the electrode before use and with the regulation of the water bath in which the potassium chloride solution was kept, it was possible to obtain readings at a temperature of 36 to 37 C in both solutions. The control readings of the buffer solution prior to and after determinations on the aqueous were carried out at approximately the same temperature.

11 The capillary electrodes were made by Frederick F. Anderson, of the department of pharmacology, Columbia University College of Physicians and Surgeons.

12 Dr. H. T. Clark, of the department of biochemistry, Columbia University College of Physicians and Surgeons, permitted the use of the constant temperature air chamber.

For the *in vivo* experiments general anesthesia was induced by the intraperitoneal injection of sodium pentobarbital, 40 mg per kilogram of body weight. A suture was inserted at the border of the upper lid after injection of a small amount of 0.1 per cent nupercaine hydrochloride. The lid was retracted by means of the suture to expose the upper portion of the limbus. The rabbit was placed on an insulated operating board, which was fitted with glass supports for the electrode assembly. The needle of the properly warmed electrode was introduced into the anterior chamber and was held in place with a hard rubber clamp, which could be adjusted by a series of joints. After adequate drainage of the aqueous through the capillary, the distal end of the capillary was connected by an agar-potassium chloride bridge to the calomel half-cell. The operating board was placed in the constant temperature air chamber, and the electrodes were connected to the potentiometer by shielded leads. The electrodes were calibrated prior to and after each measurement of the aqueous under the conditions of the experiments. The same criteria for the reliability of the readings were applied as in *in vitro* experiments.

OUTLINE OF EXPERIMENTS

Chinchilla rabbits were selected as the experimental animals. In preliminary tests the temperature in the anterior chamber was measured by a suitably formed thermocouple at a room temperature of about 26°C. An average temperature of 36.6°C was read when local anesthesia with 0.1 per cent nupercaine hydrochloride had been induced. The reading was slightly lower, 36.4°C, in rabbits under prolonged systemic anesthesia with sodium pentobarbital. These results of measurement of temperature in the anterior chamber compared well with those reported by Nelson¹³ and Kokott¹⁴. Most of the p_H determinations were performed, therefore, at about 36.5°C in a constant temperature air chamber. In a relatively large comparative series, the experiments were conducted at room temperature to obtain a conversion factor for the projected adaptation of the method for human subjects.

The study was first concerned with the influence of the various types of anesthesia on the p_H of the aqueous. For local anesthesia 1 drop of 0.1 per cent nupercaine hydrochloride (about p_H 5) was instilled three times at intervals of one minute in one eye, the same anesthetic was applied to the other eye over a period of one hour at intervals of fifteen minutes. In a small series of experiments anesthesia was induced with butacaine sulfate. For systemic anesthesia 40 mg of sodium pentobarbital per kilogram of body weight was injected intraperitoneally. Measurement of the p_H of the aqueous of one eye took place as soon as the anesthesia was deep enough, that is, after eighteen to twenty-three minutes, and that of the other eye about one hour later. Additional experiments were conducted to study the effect of ether anesthesia and that of subcutaneous injections of morphine on the hydrogen ion concentration of the aqueous.

The diet of the rabbits consisted of oats and hay. Three rabbits received a diet rich in alkali for a period of five weeks, and the p_H values of the aqueous were collated with those of rabbits on the usual diet.

13 Nelson, F. Experimenteller Beitrag zur Frage der Temperatur in der vorderen Augenkammer, insbesondere bei Anwendung des Dampfkaeters nach Wessely, *Klin Monatsbl f Augenh (Beilagehft)* **78** 48, 1927.

14 Kokott, W. Zur Frage der Kurzwellenbehandlung des Auges, Untersuchungen über die Erwärmung des Glaskörpers im Kaninchenauge bei Kurzwellenbestrahlung mit einem Rohrensender, *Klin Monatsbl f Augenh* **97** 448, 1936.

Another series of experiments pertained to the influence of a high protein content of the aqueous on its p_H . For this purpose vasodilators were introduced into the anterior chamber by iontophoresis, preliminary experiments having shown that this procedure greatly increased the proteins. Plasmoid aqueous was also produced by intravitreal infection with *Staphylococcus aureus*.

Finally, attempts were made to shift the hydrogen ion concentration by introducing anions from a solution of sodium bicarbonate by ion transfer. In relation to previous studies on iontophoresis with antibiotic substances, the p_H of the aqueous was also determined after the iontophoretic application of sulfonamide compounds and penicillin.

RESULTS AND COMMENT

The p_H of the aqueous changed significantly with the selected type of anesthesia. It varied with nupercaine anesthesia from 7.48 to 7.59, with an average of 7.53 for 24 determinations on the normal eyes of

TABLE 1— p_H of the Aqueous of Rabbits with the Eye Under Local Anesthesia

With Nupercaine Hydrochloride At Body Temperature			At Room Temperature			With Butacaine Sulfate At Room Temperature		
Rabbit Number	Brief Anesthesia		Rabbit Number	Brief Anesthesia		Rabbit Number	Control Eyes (Nupercaine)	
	OD	OS		OD	OS			
1	7.58	7.58	15	7.67	7.68	25 OD	7.54	OS 7.54
2	7.49	7.52	16	7.66	7.76	26 OD	7.54	OS 7.55
3	7.55	7.57	17	7.65	7.70	27 OD	7.58	
4	7.49	7.49	18	7.58	7.70	OS	7.59	
5	7.52	7.54	19	7.64	7.69			
6	7.53	7.53	20	7.52	7.60	Average	7.56	7.545
7	7.50	7.55	21	7.63	7.68			
8	7.49	7.50	22	7.64	7.69			
9	7.50	7.54	23	7.65	7.70			
10	7.59	7.55	24	7.60				
11	7.59							
12	7.50		Average	7.63	7.677			
13	7.53							
14	7.48							
Average	7.53							

rabbits at a temperature of 36.5 C and from 7.52 to 7.67, with an average of 7.63 for 10 eyes at a temperature of 23 C (table 1). The values were obtained after the local anesthetic had been instilled three times as described in the technic. The aqueous became on an average 0.047 p_H unit more alkaline (9 experiments) after continuation of the topical anesthesia for about one hour. When both eyes of the same animal were treated identically, the average difference between the two eyes was 0.02 p_H unit. Two local anesthetics were used, 0.1 per cent nupercaine hydrochloride, which strongly inhibits mitosis and cell migration, according to Smelser and Ozanics,¹⁵ and 2 per cent butacaine sulfate, with its moderate effect on cell division.¹⁵ No differences between

15 Smelser, G. K., and Ozanics, V. Effect of Local Anesthetics on Cell Division and Migration Following Thermal Burns of Cornea, *Arch. Ophth.* **34** 271 (Oct.) 1945.

these two anesthetics were noted, however, in respect to their influence on the p_H readings of the aqueous

The values at 36.5°C were in close agreement with those obtained electrometrically on the aqueous of rabbits by Baurmann⁴ (p_H 7.5 to 7.52) and the calculated figures of Kronfeld and others. The authors with the exception of Kubík^{5e} and Sano,¹⁶ did not specify the type of anesthesia. Whereas Kubík did not observe any effect of local cocaine anesthesia on the p_H of the aqueous, Sano reported changes in the p_H after instillation of various anesthetics and ophthalmotherapeutic solutions. In contrast to the present results, he found that cocaine decreased and that tetracaine and nupercaine increased the hydrogen ion concentration. It is doubtful whether the colorimetric method which he applied is appropriate for such investigations.

In view of the studies of Friedenwald and Buschke¹⁷ on the depressing effect of systemically administered epinephrine on the migration of the corneal epithelium and the similar experiences of Smelser¹⁸ with its topical application, the p_H of the aqueous was determined after the repeated instillation of epinephrine hydrochloride in 1/1,000 dilution. Previous studies, with conflicting results were made by Sano¹⁶ with an indicator method and by Vincent^{5f} with the hydrogen electrode. The former reported an increase and the latter a significant decrease in the hydrogen ion concentration after instillation. In the present study the technic of Vincent was followed, that is, the solution was instilled three times at ten minute intervals. Table 2 indicates that the values obtained were within the p_H range of the control eyes and were at variance, therefore, with aforementioned reports.

Despite the various effects of anesthetics and epinephrine on mitosis and migration of epithelium cells described by Buschke and his associates,¹⁹ Smelser and Ozanics¹⁵ and Friedenwald and Buschke,¹⁷ the p_H of the aqueous shifted in the same direction and degree with nupercaine hydrochloride and butacaine sulfate and remained unaffected with epinephrine. Nevertheless, the more alkaline readings of the aqueous

16 Sano, T. Experimentelle Studien über den Einfluss der pupillomotorischen Mittel auf die Wasserstoffionkonzentration des Augenkammerwassers, *Acta Soc ophth jap* **36** 1105, 1932, abstracted, *Zentralbl f d ges Ophth* **28** 473, 1933, Experimentelle Studien über den Einfluss der verschiedenen Augentropfmittel auf die Wasserstoffionkonzentration des Augenkammerwassers, *Acta Soc ophth jap* **36** 1837, 1932, abstracted, *Zentralbl f d ges Ophth* **29** 86, 1933.

17 Friedenwald, J. S., and Buschke, W. The Influence of Some Experimental Variables on the Epithelial Movements in Healing of Corneal Wounds, *J Cell & Comp Physiol* **23** 95, 1944.

18 Personal communication to the authors.

19 Buschke, W., Friedenwald, J. S., and Fleischmann, W. Studies on the Mitotic Activity of the Corneal Epithelium, *Bull Johns Hopkins Hosp* **73** 143, 1943.

of rabbits with local anesthesia, especially after prolonged topical anesthesia, can best be explained by the increase in permeability of the cornea due to epithelial damage. In their studies on the gaseous exchange through the cornea, Fischer²⁰ and Redslob and Tremblay²¹ found that the cornea had a unidirectional permeability for carbon dioxide and oxygen. Fischer assumed that carbon dioxide passed through the cornea from the aqueous into the surrounding atmosphere and expressed the belief that the epithelium is a partial barrier for these two gases, since they pass through the normal epithelium to a moderate degree. The escape of carbon dioxide facilitated by the enhanced permeability of the cornea with topical anesthesia, therefore, may be the cause of the relative alkalinity.

TABLE 2—*p_H of the Aqueous* After Instillation of Epinephrine, Injection of Morphine and Use of Alkali-Rich Diet*

Procedure	Rabbit No	Treated Eye	Control Eye
Epinephrine hydrochloride (1:1000), 2 drops instilled every ten minutes for ½ hour	23	7.63	7.62
	29	7.65	7.67
	30	7.69	7.65
	Average	7.63	7.65
Morphine sulfate 10 Mg/kg subcutaneously	31	7.66	7.66
	32	7.42†	7.51
	33	7.60	7.62
	34	7.61	7.64
Alkali rich diet	Average	7.58	7.607
		OD	OS
	35	7.64	‡
	6	7.65	‡
Average	37	7.59	7.64
		7.63	

* Determined with local nupercaine anesthesia at room temperature

† Deep depression of respiration

‡ Readings not reliable

General anesthesia induced with a barbiturate had the converse effect on the hydrogen ion concentration of the aqueous humor (table 3). The average of 4 readings recorded after a brief general anesthesia with sodium pentobarbital was 7.495, but the p_H shifted to the acid side, 0.04, with the continuation of the anesthesia. When the *in vivo* technic was used, the average p_H was 7.44 about twenty minutes after the injection of sodium pentobarbital (7 eyes) and 7.4 about one hour after the injection (8 eyes). Except for 1 eye, the readings at a

20 Fischer, F. P. Ueber den Gasaustausch der Hornhaut mit der Luft, Arch. Augenh. **120** 146, 1930.

21 Redslob, E., and Tremblay, J. L. Etude sur les échanges gazeux à la surface de l'oeil, Ann. d'ocul. **170** 415, 1933.

later period indicated a change to the acid side as the depth and the duration of anesthesia increased. This shift was probably due to the usually pronounced depression of the respiratory center and the ensuing accumulation of carbon dioxide.

In vivo experiments gave slightly less alkaline readings than experiments on aspirated aqueous with the animal under pentobarbital anesthesia. This difference can be accounted for by the fact that a deeper anesthesia, and therefore a greater depression of the respiratory center, was necessary in the in vivo experiments to restrain the animal from undue movements. Another possible explanation is that of the escape of carbon dioxide from the measuring capillary in

TABLE 3— p_H of the Aqueous of Rabbits Under General Anesthesia

With Sodium Pentobarbital											
In Vitro									With Ether In Vitro		
In Vivo			At Body Temperature				At Room Temperature		At Room Temperature		
Rab bit No	p_H OD Deter- mined 18 23 Min After Initia- tion of Anes- thesia	p_H OS Deter- mined 45-120 Min After Initia- tion of Anes- thesia	Rab bit No	p_H OD Deter- mined 10 35 Min After Initia- tion of Anes- thesia	p_H OS Deter- mined 30 60 Min After Initia- tion of Anes- thesia	Rab bit No	p_H OD Deter- mined 10 20 Min After Initia- tion of Anes- thesia	p_H OS Deter- mined 17 60 Min After Initia- tion of Anes- thesia	Rab bit No	p_H OD Deter- mined 5 Min After Initia- tion of Anes- thesia	p_H OS Deter- mined 15 Min After Initia- tion of Anes- thesia
38	7 44	7 39	47	7 48	7 46	51	7 59	7 53	56	7 53	7 51
39	7 47	7 41	48	7 49	7 43	52	7 60	7 54	57	7 59	7 57
40	7 43	7 39	49	7 48	7 45	53	7 56	7 46*	58	7 53	7 48*
41	7 43	7 38	50	7 53	7 48	54	7 63	7 49	59	7 55	
42	7 46	7 43				55		7 50			
43	7 44	7 44	Aver	7 495	7 455				Aver	7 56	7 53
44	7 42					Aver	7 595	7 50			
45		7 41									
46		7 38									
Aver	7 44	7 40									

* Asphyxia

the brief period between the withdrawal of the needle and its blocking with an agar-potassium chloride disk in the in vitro technic. This explanation was disproved by the fact that the omission of the disk did not result in an increase in the p_H .

Whereas many investigators have found that systemic anesthesia induced with the barbiturates has little influence on the tissue and blood, the present study shows that this observation cannot be extended to a body fluid like the aqueous with a moderate buffering capacity. Experiments with ether anesthesia (7 eyes) supported the theory that the accumulation of carbon dioxide was operative in a shift of the p_H to the acid side, since a similar increase in the hydrogen ions was observed only when the animal had sustained a period of asphyxia (rabbit 58). An analogous trend was noted in a small series of

experiments with the subcutaneous injection of 10 mg of morphine sulfate per kilogram of body weight, as in 1 of the 4 rabbits in which the respiration was obviously impaired the injection resulted in an increase in the hydrogen ion concentration of the aqueous (table 2)

In conclusion, the physiologic values of the p_H of the aqueous in rabbits can be considered in the range of 7.44 to 7.49, that is, at the beginning phase of general anesthesia with a barbiturate and before marked depression of the respiratory center has occurred. Both local and systemic anesthesia alter the p_H of the aqueous, especially when prolonged. It is desirable, therefore, to specify in reports on the p_H of the aqueous the type of anesthesia employed. Conclusions based on the effect of barbiturate anesthesia on the p_H of the aqueous can be extended to the vitreous, it is highly probable that the physiologic p_H of the vitreous, which could be measured only *in vivo* with deep barbiturate anesthesia, is more alkaline (p_H 7.1 to 7.2) than has previously been reported (p_H 7.0 to 7.1¹). A more detailed discussion of the relation of the hydrogen ion concentration of the aqueous and vitreous humors will be included in a later study on the p_H of both fluids of the same eye.

✓ Kronfeld^{5d} in a study on the carbon dioxide content of the aqueous in rabbits reported that it was influenced by the amount of alkali in the diet. He found that food rich in alkali led to an increase of the carbon dioxide content of the aqueous from 56.1 to 61.5 volumes per cent. An alkali-rich diet, similar to that used by Kronfeld, and consisting of leafy vegetables and bread, did not cause any noticeable change in the p_H of the aqueous (table 2). The values obtained in 4 determinations (3 rabbits) did not differ significantly ✓ from those obtained on animals with the usual oats and hay diet.

For the study of the relation of the protein content of the aqueous to its p_H , a considerable increase of protein was achieved by the iontophoretic introduction of histamine and physostigmine. One hour after an aqueous solution of 0.1 per cent histamine phosphate and 0.1 per cent physostigmine salicylate was applied for one minute at 1 milliamperes from the anode, a sample of aqueous was withdrawn and the protein content determined with a modified nephelometric adapter in a Coleman spectrophotometer. It varied from 250 to 341 mg per hundred cubic centimeters, with an average of 277 mg per hundred cubic centimeters for 11 samples. Determinations on this plasmoid aqueous revealed that its p_H did not differ from that of untreated (control) eyes with a protein content of 20 to 50 mg per hundred cubic centimeters (table 4).

It was previously reported that an experimental intravitreal infection, produced by the injection of a mannitol-fermenting strain of *Staph aureus* and of *Diplococcus pneumoniae*, type III was accompanied

in an early stage with a local acidosis of the vitreous with p_H readings between 5.7 and 6.35. A similar staphylococcal infection of the vitreous caused, however, only a slight increase (0.07 p_H unit) in the hydrogen ion concentration of the aqueous. Its extent corresponded roughly to the development of the clinical signs of inflammation in the anterior segment. In table 4 are reported the measurements which were made twenty-four hours, forty-eight hours and one week after the infection. As determinations of the p_H were not made on the vitreous of these eyes, but are planned for a later study, the relation between the respective values of the hydrogen ion concentration in the two intra-ocular fluids will not be dealt with here. It is apparent, however, that the p_H of the aqueous is but little affected by the coexistence with an acute infection of the vitreous.

Meesmann^{2f} did not observe a change in the p_H of the aqueous associated with inflammation whereas Pignolosa^{3h} reported an increase

TABLE 4— p_H of the Aqueous* With an Increase in Protein

Due to Vasodilators Both Eyes Treated			Due to Vitreal Infection with Staphylococcus Aureus								
Rab bit No	OD	OS	Rab bit No	24 Hr After Infection	Control Eye	Rab bit No	48 Hr After Infection	Control Eye	Rab bit No	One Week After Infection	Control Eye
60	7.51	7.51	63	7.47	7.58	66	7.46	7.50	69	7.41†	7.57
61	7.54	7.52	64	7.42	7.48‡	67	7.52	7.53	70	7.57	7.58
62	7.53	—	65	7.47	7.59	68	7.45	7.58	71	7.38†	7.43‡
Aver	7.53	7.515		7.45	7.55		7.48	7.54		7.45	7.53

* Determined with local nupercaine anesthesia at room temperature

† Pronounced hyperemia and swelling of iris

‡ Scarred and vascularized cornea

of the hydrogen ion concentration of the aqueous of rabbits with an experimental tuberculous infection of the uvea and expressed the belief that the development of a complicated cataract, which he observed in many instances, was possibly dependent on this shift. Although this author's observations are in accord with those reported here, his results are not conclusive because of the use of the hydrogen electrode with a plasmoid aqueous.

Mawas^{5c} suggested that local, noncompensated acidosis associated with certain types of glaucoma might be counteracted by ionization with alkalis. To our knowledge, this suggestion has not led to investigations on the influence of iontophoresis on the p_H of intra-ocular fluids. In the present study, such measurements were carried out after the iontophoretic introduction from the cathode of a 5 per cent solution sodium bicarbonate applied at a strength of 2 milliamperes for ten minutes and a 5 per cent solution of sodium sulfadiazine and 5,000 Oxford units of sodium penicillin per cubic centimeter applied

at a strength of 2 milliamperes for five minutes. Under the conditions of the experiment, none of the introduced anions caused a significant change in the p_H of the aqueous (table 5). It is probable

TABLE 5— p_H of the Aqueous * After Iontophoresis

Procedure	Rabbit No	Treated Eye	Control Eye
5 per cent sodium bicarbonate 2 ma, 10 minutes	72	7.68	7.66
	73	7.6-7.3	7.62
		Drifting	
	74	7.61	7.60
	75	7.64	7.61
Average		7.64	7.61
5 per cent sodium sulfadiazine, 2 ma, 5 minutes	76	7.62	7.62
	77	7.57	7.57
	78	7.57	7.59
		7.59	7.59
Average		7.59	7.59
Sodium penicillin, 5,000 Oxford units per cc, 2 ma, 5 minutes	79	7.64	7.60
	80	7.72	7.65
	81	7.62	7.64
	82	7.61	7.61
	83	7.62	7.63
Average		7.64	7.63

* Determined with local nupercaine anesthesia at room temperature

that the ionic equilibrium was retained by a compensatory egress of anions by various channels under the influence of the impressed voltage.

SUMMARY

1 A capillary glass electrode was designed to determine the hydrogen ion concentration of the aqueous of rabbits in vitro and in vivo at a physiologic temperature.

2 With this electrode the average physiologic p_H of the rabbit aqueous was 7.53 with brief local anesthesia and between 7.44 and 7.49 in the initial stage of systemic anesthesia.

3 Prolongation of topical anesthesia was followed by a slight increase in the p_H . Lengthy general anesthesia led to a significant decrease in the p_H . A similar shift to the acid side was noted after asphyxia during anesthesia with ether and after pronounced depression of the respiratory center with morphine.

4 Ectogenous infections of the vitreous with *Staph aureus* caused a moderate shift of the hydrogen ion concentration of the aqueous to the acid side.

5 A diet rich in alkali, an increase in the protein of the aqueous and the iontophoretic introduction of anions had no noticeable effect on the p_H of the aqueous.

TREATMENT OF CHRONIC BLEPHAROCONJUNCTIVITIS WITH PENICILLIN OINTMENT

Report of Twenty-Five Cases

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THE HISTORY of penicillin is essentially the story of two developments. The first was Fleming's accidental discovery of the inhibitive effect of *Penicillium notatum* on staphylococci in vitro¹. Clutterbuck, Lowell and Rainstrick, stimulated by Fleming's study, attempted to extract penicillin in 1932, but their efforts were largely unsuccessful.

Second, through the extraction method, involving the passing of impure acid penicillin broth from the watery solution into an organic solvent (ether or amyl acetate) and the subsequent passing of the purified agent again into water (shaken with alkali), Florey and his colleagues showed how to obtain sufficient penicillin in a relatively pure form and demonstrated its clinical use².

METHOD OF ASSAY

As the exact constitution of penicillin has not yet been worked out, the material cannot be standardized by chemical means. However, the success of research largely depended on a reliable procedure for assay. The method adopted was worked out by Dr. Norman Heatly, whereby penicillin is assayed by its biologic effect. The Florey (Oxford) unit—the amount of penicillin as compared with an arbitrary standard which completely inhibits the growth of a test strain of *Staphylococcus aureus*—is still used and probably will hold its place until a chemically standardized product is available. In Florey's original material there were 40 to 50 units per milligram (Abraham and others³). Material which runs to 1,000 units per milligram has now been prepared.

TOXICITY AND ANTIBACTERIAL ACTION

The relative lack of toxicity of penicillin for most tissues was apparent to Fleming¹ and to Florey and his associates². Further studies carried

1 Fleming, A. On the Antibacterial Action of Cultures of *Penicillium*, with Special Reference to Their Use in Isolation of B. Influenzae, *Brit J Exper Path* **10** 226 (June) 1929.

2 Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Saunders, A. G. Penicillin as a Chemotherapeutic Agent, *Lancet* **2** 226 (Aug. 24) 1940.

3 Abraham, E. P., and others. Further Observations on Penicillin, *Lancet* **2** 177 (Aug. 16) 1941.

out by Herrell and his associates⁴ revealed that penicillin was a highly antibacterial substance and had low toxicity as measured by tissue culture methods

In evaluating the action of penicillin against infection in vivo, the anatomic site that lends itself best to treatment must be determined. Therefore, in treatment of ocular infections, the first step is to determine the concentration reached in the cornea by the various means of administration. Although von Sallmann and associates⁵ have shown that penicillin enters the aqueous humor of the normal eye after application of the substance in a cup bath to the eye for five minutes, the present biologic methods of estimating the concentration of the drug make such a determination in corneal tissue most difficult. Bellows⁶ has published his results on determination of the concentration of penicillin in the cornea and the conjunctiva. Later, von Sallmann and his associates⁷ found that a 0.25 per cent solution of penicillin sodium penetrated the anterior segment of the eye. The local application of penicillin proved to be more effective than intramuscular administration in the treatment of corneal infections due to a gram-negative bacillus (Leopold, Holmes and LaMotte⁸).

BACTERIAL SENSITIVITY

The degree of sensitivity of the species of the infecting organism to the drug is but one of a number of factors which influence the therapeutic result. Also of importance are initial differences in sensitivity of strains of the same species to the selected compound and subsequent differences developing during the period of treatment, due in part to the maturation of the bacteria. Other factors are the number and the virulence of the infecting organisms, the amount of protein breakdown products or pus and the quality of the cellular and humoral body defenses.

4 Heilman, D. H., and Herrell, W. E. Comparative Antibacterial Activity of Penicillin and Gramicidin. Tissue Culture Studies, Proc. Staff Meet., Mayo Clin. **17** 321 (May 27) 1942, Comparative Bacteriostatic Activity of Penicillin and Gramicidin, abstracted, J. Bact. **43** 12 (Jan.) 1942. Herrell, W. E., Nichols, D. R., and Heilman, D. H. Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with Analysis of 150 Cases in Which It Was Employed, J. A. M. A. **125** 1003 (Aug. 12) 1944.

5 von Sallmann, L., Meyer, K., and Di Grandi, J. Penetration of Penicillin into the Eyes, Arch. Ophth. **31** 1 (Jan.) 1944.

6 Bellows, J. G. Penicillin Therapy in Ocular Infections, Am. J. Ophth. **27** 1206 (Nov.) 1944.

7 von Sallmann, L., Meyer, K., and Di Grandi, J. Experimental Study on Penicillin Treatment of Ectogenous Infection of Vitreous, Arch. Ophth. **32** 179 (Sept.) 1944.

8 Leopold, I. H., Holmes, L. F., and LaMotte, W. O., Jr. Local Versus Systemic Penicillin Therapy of Rabbit Corneal Ulcer Produced by Gram-Negative Rod, Arch. Ophth. **32** 193 (Sept.) 1944.

Some of these factors cannot be evaluated at all, and others require time-consuming tests. The complication of crossed mixed infection in ocular diseases is not so important as in general infections but may retard recovery. There is evidence suggesting that with the elimination of a virulent penicillin-sensitive organism in a given case the remaining, nonsensitive organisms are not very pathogenic.

More than twenty bacteria clinically sensitive to penicillin have been described. The following penicillin-sensitive pathogens are encountered in ocular diseases: the alpha, beta and gamma streptococci, *Staphylococcus aureus* and *Staphylococcus albus*, *Neisseria gonorrhoeae*, *Neisseria intracellularis*, *Corynebacterium diphtheriae* (mitis), *Clostridium welchii*, *Actinomyces bovis*, *Treponema pallidum*, and diphtheroids. Grouped according to sensitivity to penicillin, the most highly sensitive organisms are the (beta) hemolytic streptococci, the gonococcus and some strains of staphylococci. The viridans (alpha) type of streptococcus, the nonhemolytic (gamma) streptococcus and the remaining organisms are less sensitive. Staphylococci vary from extreme sensitivity to extreme resistance.

Although gram-negative rods are insensitive to the action of penicillin, a few species are moderately susceptible, and still others exhibit a slight degree of sensitivity.⁸ Abraham and his co-workers⁹ showed that *Salmonella enteritidis* (gartneri) was inhibited by a 1:20,000 dilution, and *Salmonella typhi* by a 1:10,000 dilution of a solution of penicillin which inhibited a culture of *Staph aureus* when diluted 1:1,000,000.

In the experience of Fleming¹, Hobby, Meyer and Chaffee⁹, McKee and Rake,¹⁰ and von Sallmann and Di Grandi,¹¹ members of the Friedlander group of bacilli have been insensitive to penicillin. However, Smith¹² showed that variation in strains is remarkable in this group, and the sensitive strains which he encountered included some of type A. A similar situation was reported by Churchman¹³ in that among gram-negative rods, on the whole insensitive to the action of methylrosaniline chloride, an occasional strain may be encountered.

Penicillin should be given preference also in the treatment of infections due to streptococci and sensitive staphylococci. Some strains of

9 Hobby, G. L., Meyer, K., and Chaffee, E. Activity of Penicillin in Vitro, *Proc Soc Exper Biol & Med* **50** 277 (June) 1942.

10 McKee, C. M., and Rake, G. Biological Experiments with Penicillin, *J Bact* **43** 645 (May) 1942.

11 von Sallmann, L., and Di Grandi, J. Simultaneous Local Application of Penicillin and Sulfacetimide, *Arch Ophth* **32** 190 (Sept) 1944.

12 Smith, L. D. The Bacteriostatic Agent of *Penicillium Chrysogenum*, *J Franklin Inst* **254** 396, 1942.

13 Churchman, J. W. Further Studies on Behaviour of Bacteria Toward Gentian Violet, *J Exper Med* **33** 569 (May) 1921.

staphylococci are resistant to penicillin. If the resistant bacteria were responsible for the virulence of the infection, penicillin therapy was less beneficial.

One of the requirements for successful treatment of bacterial infections with penicillin is limitation of its use to infections due to pathogens which are known to be susceptible. Therefore great care has to be exercised in appraising the value of penicillin in a given ocular infection. The unavoidable error of clinical observation is high. Many ocular diseases are self limiting. Any therapeutic agent employed in such a disease may be credited erroneously with expediting recovery or producing a cure. Conversely, the possibility of desensitization of a strain of staphylococci found in the eyelids and conjunctiva by previous penicillin therapy has to be considered.

PREPARATION AND DOSAGE

Through the large scale American production, penicillin is supplied in sealed glass bottles as a sodium salt. It has a brown or yellow granular appearance and is extremely soluble in water and in saline or dextrose solution. However, the material is unstable in air and very hygroscopic, its potency being impaired by heat and in acid mediums.^{13a} Therefore the sealed ampules must be preserved in the refrigerator until used. A day's dose made up in the proper solution may be safely kept in the cold container.

In topical application the Committee on Chemotherapy has recommended solutions containing 250 or 500 units per cubic centimeter. However, no untoward effect has been observed from the use of concentrations far greater than those mentioned, and very possibly better results will be obtained with the use of stronger solutions. Significantly, it is not the purpose of this paper to discuss the unsettled question of adequate penicillin dosage. Excellent results have been reported with relatively small quantities of the material but this does not rule out the need of larger doses in some cases (Herrell,¹⁴ Bloomfield and associates¹⁵).

Owing to the impracticability of continuous therapy with solutions of penicillin in overseas units, with the instability at room temperatures, another form of preparation of the substance was indicated in order to

13a However, the material is unstable in air and very hygroscopic, its potency being impaired by heat and in acid mediums (Abraham, E. P., Chain, E. and Holiday, E. R. Purification and Some Physical and Clinical Properties of Penicillin, *Brit J Exper Path* **23** 103 [June] 1942)

14 Herrell, W. E. The Clinical Use of Penicillin. An Antibacterial Agent of Biologic Origin, *J A M A* **124** 622 (March 4) 1944

15 Bloomfield, A. L., Kirby, W. M. M., and Armstrong, C. D. A Study of "Penicillin Failures," *J A M A* **126** 685 (Nov 11) 1944

obtain prolonged therapeutic action of penicillin of sufficient concentration in the eyes and at the same time to preserve its potency for a moderately long period at room temperature. After various unsuccessful research studies were made with the idea of incorporating some preservative, it was decided to dissolve the penicillin in an ophthalmic water-soluble ointment. Thus, a soluble ointment as a base for the penicillin was prepared, consisting of wool fat U S P, 17 per cent, white petrolatum U S P 51 per cent, distilled water, 5 per cent, and light liquid petrolatum U S P 22 per cent. In the additional 5 per cent of distilled water 100,000 Oxford units of penicillin was dissolved and then incorporated into 7 Gm of the ointment. A small bead of penicillin ointment tested *in vitro* on a nutrient agar cup plate seeded with staphylococci produced an inhibition ring 50 mm in diameter. After five weeks at room temperatures in the tropics, the penicillin ointment produced an inhibition ring 44 mm in diameter. With this result, it is reasonably safe to state that penicillin ointment for all practical purposes is stable for at least one month at room temperatures. These results are in accord with those of Keyes,¹⁶ who has gone further and obtained a penicillin ointment which has a stability of six months, the ointment however, being kept in a commercial refrigerator.

The stronger penicillin ointment was decided on in order to determine the efficiency of a more potent single daily application of penicillin. Such a method of administration had an advantage, as the patients were combat troops. After repeated quantitative measurements, it was determined that each application contained 700 to 800 Oxford units.

Florey and Florey,¹⁷ Cashell,¹⁸ Bellows⁹ and others reported encouraging results in treating infections of the border of the lid and the conjunctiva with ointments containing penicillin.

Although all types of ocular infection were treated, this paper will limit itself to a report on a series of 25 cases of chronic blepharoconjunctivitis.

REPORT OF CASES

CASE 1—This case is typical of 7 cases.

A man aged 35 reported on Dec 10, 1944, complaining of scaling of both eyelids and bilateral irritative conjunctivitis. Intense lacrimation had interfered with his duties in the Air Corps for three months. At another base, prior to transfer to this hospital, he had received a course of treatment with 5 per cent ophthalmic sulfathiazole ointment, with only temporary relief. Vision was 20/20 in each eye, with ability to read Jaeger type 1. Examination revealed severe chronic blepharoconjunctivitis, with scales on the upper and lower lids.

16 Keyes, J E L. Penicillin in Ophthalmology, J A M A **126**:610 (Nov) 1944.

17 Florey, M E, and Florey, H W. General and Local Administration of Penicillin, Lancet **1**:387 (March 27) 1943.

18 Cashell, G T W. Treatment of Ocular Infections with Penicillin Brit M J **1** 420 (March 25) 1944.

of both eyes and an injected palpebral and bulbar conjunctiva, with annoying laceration. Culture revealed *Staph aureus*. Single daily applications of penicillin ointment was instituted. Within forty-eight hours absence of scales was noted, and the conjunctival irritation was less intense. Twenty-four hours later the redness and swelling of the lid margins had subsided to a notable degree. After one week's treatment all signs and symptoms had disappeared. Examination three weeks later, before the patient was transferred to another base, revealed no residual evidence of the original infection.

CASE 2—This case is typical of 3 cases

A man aged 26 reported on Dec 12, 1944, complaining of the typical symptoms of bilateral chronic blepharoconjunctivitis, of eight weeks' duration. Culture revealed the presence of staphylococci. Vision was 20/30 in each eye, with a correction of +0.50 D cyl, axis 90, it was 20/20, with ability to read Jaeger type 1. As the two eyes were involved equally, it was decided to use the penicillin ointment in the right eye and 5 per cent ophthalmic sulfathiazole ointment in the left eye. Single daily applications for eight days relieved the condition in the right eye, with elimination of swelling and redness of the margins of the lids. Although the left eye felt better, the redness and swelling of the lid margins persisted, and a few scales on the eyelashes were noted. After an interval of one week without treatment, the right eye was still free of infection, while the left eye continued to show a few scales and the presence of infection.

CASE 3—This case is typical of 5 cases

A man aged 23 appeared on Dec 13, 1944 with bilateral chronic blepharoconjunctivitis, of ten years' duration. Vision was 20/20 in each eye, with ability to read Jaeger type 1. In the past he had received treatment with aqueous brilliant green and 5 per cent ophthalmic sulfathiazole ointment, with only partial relief. Treatment with penicillin ointment was instituted, after four days with single daily applications all irritation in both eyes had disappeared, and within two weeks all evidence of the infection was absent. The culture, which was positive for *Staph aureus*, became negative within seventy-two hours. Examination two weeks later revealed no evidence of the original infection.

CASE 4—This case is typical of 2 cases

A man aged 27 reported on Dec 20, 1944, complaining of the usual signs and symptoms of bilateral chronic blepharoconjunctivitis. The condition was of three months' duration. Vision was 20/20 in each eye, with ability to read Jaeger type 1. Culture revealed *Staph aureus*. With the first application of the penicillin ointment to both eyes, the patient immediately complained of a severe burning sensation, with laceration and marked blepharospasm of both eyes. The conjunctiva shortly thereafter appeared greatly congested, with redness of the margins of the lids. Since an allergic reaction was suspected, patch tests were made on both forearms with the penicillin solution, the penicillin ointment and the ointment base. Twenty-four hours later positive reactions were obtained to both the ointment and the penicillin solution. A fresh penicillin ointment was prepared, with care to eliminate any possibility of impurities. The patch test with this freshly prepared ointment gave a negative reaction. Single daily applications of this ointment resulted in complete removal of the infection within twelve days.

CASE 5—This case is typical of 6 cases

A man aged 30 reported on Dec 25, 1944, complaining of bilateral chronic blepharoconjunctivitis, of six weeks' duration. Vision was 20/20 in each eye,

with ability to read Jaeger type 1. Culture revealed *Staph aureus* and *Str viridans*. Daily single applications of penicillin ointment in the right eye and of 5 per cent sulfathiazole ointment in the left eye, for twelve days, resulted in complete elimination of all signs of the infection in both eyes. Examination two weeks later showed no evidence of the infection in either eye.

Summary—The data on the 25 cases may be summarized as follows:

Age range	19 to 45 years
Duration of disease	2 to 120 months
Duration of treatment	7 to 20 days
Penicillin and sulfathiazole ointments equally effective	6 cases
Penicillin ointment more effective	17 cases
Reactions	2 cases
No improvement with penicillin ointment	2 cases
Duration of observation	1 to 2 months
Cultures demonstrating <i>Staph aureus</i>	16 cases
Cultures demonstrating <i>Staph aureus</i> and <i>Strep viridans</i>	6 cases
Cultures demonstrating <i>Staph aureus</i> and nonhemolytic streptococcus	3 cases

COMMENT

Although penicillin in solution is very unstable at room temperatures, its incorporation into an ointment base makes available an ointment which remains potent for four to five weeks at room temperatures, without doubt an effective drug to be added to the armamentarium for ophthalmic therapy. According to the results in this series of 25 cases, the ointment is more effective than drugs formerly used in the treatment of chronic blepharoconjunctivitis due to sensitive staphylococci, with rapid relief of symptoms and clearing of the infection.

Pyle and Rattner¹⁹ and Keyes¹⁰ reported cases in which allergic reactions to penicillin occurred in treatment of ocular infections. In 2 cases what originally was suspected to be an allergic response proved to be due to impurities in the ointment base.

In 6 cases equal improvement was obtained with penicillin ointment and with 5 per cent sulphathiazole ointment. Examination three weeks later showed no evidence of recurrence in the 6 patients treated with the two ointments, the eyes remaining free of infection after cure for at least one month's observation.

In the 2 cases in which no improvement resulted, the question of a noninfectious process, such as allergy, has to be considered.

CONCLUSION

A definitely potent ophthalmic penicillin ointment not requiring refrigeration is available.

Although not a panacea, the ophthalmic penicillin ointment has a decided advantage over drugs formerly used in the treatment of chronic blepharoconjunctivitis.

There was no evidence of an allergic reaction to penicillin in the present series of 25 cases.

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19 Pyle, H. D., and Rattner, H. Contact Dermatitis from Penicillin, *J. A. M. A.* **125** 903 (July 29) 1944.

HEREDODEGENERATIVE DISEASES OF THE RETINA

An Attempt at Classification

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ABIOTROPHY

IN A lecture published in the *Lancet* in 1902, Gowers¹ spoke of "death" as having two aspects. There is death of the whole body, somatic death, but there is also death of parts of the body.

Some of them may slowly die, while the life of all the rest goes on without impairment. They may die from many causes, some early, inevitably, from a grave defect of vital endurance, some much later, the failure being only slightly premature, and some at various times, apparently from various causes. When the failure is early it is often due only to a defect in vitality, a defect which seems to be inherent, the tendency thereto inborn. We do not, indeed, apply the word "death" to this slow decay of the elements, we speak of it as "degeneration," but the process is in many cases, perhaps in most, an essential failure of vitality and I think it is instructive to consider the degenerations in this aspect. But in doing so I am met by the difficulty that we have no word by which to designate this conception—a degeneration or decay in consequence of a defect of vital endurance¹.

Gowers took the word *biotrophos*, which he found had been used by an ancient writer in the sense of "vital nutrition." By prefixing the negative particle, he coined the word "abiotrophy" for the diseases characterized by "a degeneration or decay in consequence of a defect of vital endurance."

Collins² used Gowers' term "abiotrophy" to characterize certain diseases of the eyes, including retinitis pigmentosa and macular degeneration, which, he assumed, were due to a degeneration in consequence of a vital defect.

HEREDODEGENERATION AND HEREDOCONSTITUTIONAL DISEASE

However, many investigators found objections to the term "abiotrophy." The word appeared clumsy, and its etymologic derivation was not clear. According to some, it simply meant premature senility, for which an additional term was not necessary, and it added nothing to the understanding of any disease. Diseases due to a defect in vitality

1 Gowers, W. R. A Lecture on Abiotrophy, *Lancet* 1 1003, 1902.

2 Collins, E. T. Abiotrophy of the Retinal Neuroepithelium, or "Retinitis Pigmentosa," *Tr. Ophth. Soc. U. Kingdom* 39 165, 1919, Hereditary Ocular Degenerations. *Ophthalmic Abiotrophies*, *Tr. Internat. Cong. Ophth.* 1 103, 1922.

attack especially the central nervous system Jendrassik,³ who discussed these diseases of the nervous system in a number of publications, spoke of them as hereditary degenerations and created the concept of heredodegeneration This term, used practically in the same sense in which Gowers used "abiotrophy," seems to be free from some of the connotations which accompany the latter Behr⁴ made use of it in speaking of heredodegeneration of the macula

Kehrer⁵ also preferred "heredodegeneration" to "abiotrophy" and used the term for those hereditary diseases of the nervous system which in the main are characterized by a progressive loss of a specific neural tissue He expressed agreement with Bielschowsky that under the concept of heredodegeneration should be included conditions in which there is a progressive loss of elements of neural tissue, such as ganglion cells or glia cells Kehrer also pointed out that in some diseases in which a hereditary vital defect exists there is no progressive loss of tissue and the disease remains stationary for many years and perhaps throughout life He spoke of these disturbances as "heredoconstitutional" and differentiated them from the progressive "heredodegenerations"

HEREDODEGENERATIONS OF THE RETINA

Among the diseases of the retina are a number which must be classified as heredodegenerations They have this in common They are bilateral, they are hereditary and familial, they are not due to any external cause, to inflammation or to vascular changes, with the exception of the heredoconstitutional diseases, they are progressive Because the elements of the retina are neural or of neural origin, they frequently partake of the heredodegenerative diseases which affect similar elements in the central nervous system An attempt to classify the heredodegenerative diseases which affect the retina must take into account the fact that the retina is made up of a number of separate elements and that each of these elements is theoretically subject to some form of heredodegeneration A review of the various diseases of the retina shows that this is actually the case and that the degenerations of the retina can be classified according to the individual layer or kinds of cells primarily affected The layers of the retina thus subject to some form of heredodegeneration are 1 The elastic layer of Bruch's membrane This membrane, although not a part of the retina, is a border membrane

3 Jendrassik, E Die hereditären Krankheiten, in Lewandowski, M Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol 2, p 321

4 Behr, C Heredodegeneration der Makula, Klin Monatsbl f Augenh 65 465, 1920

5 Kehrer, F Erbliche organische Nervenkrankheiten Allgemeine Einleitung, in Bumke, O, and Foerster, O Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol 16, p 222

forming a barrier between the choroid and the retina. It is subject to degeneration which has consequences for the retina. 2 The pigment epithelium. 3 The neuroepithelium. 4 The nuclear layers. 5 The ganglion cells. 6 The nerve fiber and the glia cells.

Glass Membrane of Bruch—This membrane consists of two distinct layers: an inner one, which is a product of the pigment epithelium, and an outer elastic layer, which is in immediate touch with the choriocapillaris. The elastic layer forms the termination of the intertwined elastic and collagenous fibrils of the choroid. This layer is subject to degeneration, which shows itself by a change in its staining characteristics and by changes in its width, becoming thickened in some places and thinned in others, to the point of rupture and hole formation. The degeneration causes secondary changes and results in two distinct diseases:

1 Disciform degeneration of the macula (Kühnt-Junius disease), in which the primary degeneration is limited to the elastic layer of Bruch's membrane.

2 Angioid streaks in the fundus, in which, in addition to the primary degeneration in the elastic layer, there occurs frequently a degeneration of the elastic tissue of some areas of the skin (pseudoxanthoma elasticum) and of the elastic tissue in some blood vessels.

Pigment Epithelium—I have said that the inner, or basal, layer of Bruch's membrane is a product of the pigment epithelium. In this layer there occur hyaline or colloid bodies, known as such or by the German name of drusen. These hyaline or colloid bodies are of degenerative character. They occur (1) in inflammatory diseases of the eyes, (2) in association with other heredodegenerative diseases of the retina, (3) in advanced age and (4) in young persons. Whenever they occur in the absence of inflammatory diseases, in young or older persons by themselves or in association with other heredodegenerative diseases of the retina, they are the result of a primary vital defect on a hereditary basis of the pigment epithelium.

Neuroepithelium—The neuroepithelium is functionally divided into the central, or macular, area and the extramacular, or peripheral, area. Each of these areas is subject to heredodegeneration, which affects them separately or in combination, alone or in association with heredodegenerative diseases of the central nervous system. The neuroepithelium is the seat of typical examples of heredodegeneration, or abiotrophy. Here the retinal elements which have developed begin to disappear at various periods in life.

Central, or Macular, Area—Degeneration of this area has been described under various names: Hutchinson-Tay choroiditis, familial choroiditis or honeycomb choroiditis, Best's familial congenital

macular degeneration, Stargardt's familial progressive degeneration in the macula and Lutz's hereditary familial chorioretinitis. The multiplicity of names has led to the assumption that the macular area is affected by a number of different degenerative diseases. It is to the credit of Behr that he clarified the situation by showing that all these various familial and hereditary diseases of the macular area constitute one group—heredodegeneration of the macula. He found that (1) all these conditions present a uniform and characteristic picture, (2) that underlying the clinical picture is a familial and hereditary degeneration of the macula, (3) that the age at which the disease manifests itself varies in the different families and that it usually occurs at the age of 6 to 8 years (infantile type), of 12 to 14 years (juvenile type), in the twenties (adult type), in the late forties and early fifties (presenile type) and still later (senile type) and (4) that the disease appears either alone or in combination with other diseases of the retina or of the central nervous system.

Hereditary degeneration of the macular area can therefore occur (1) alone or in association with (2) degeneration of the peripheral areas of the retina, (3) atrophy of the optic nerve, (4) color blindness or (5) mental deterioration.

These combinations do not constitute separate forms of macular degeneration. In them there are distinct hereditary diseases which occur in association, a not uncommon occurrence in the central nervous system.

Extramacular Neuroepithelium—The typical heredodegenerative disease of the extramacular neuroepithelium is retinitis pigmentosa. The disappearance of the rods and cones begins in the region of the equator and proceeds centrally. It is the disease which Collins used to illustrate abiotrophy of the retinal elements. Retinitis pigmentosa is inherited in three modes: (1) as a recessive, the most frequent mode in heredity, (2) as a dominant, which is much less frequent, and (3) as a sex-linked recessive, which is rare. The disease occurs alone or in association with other forms of heredodegeneration: (1) degeneration of the macular area, (2) color blindness, (3) deafness, (4) mental deterioration, (5) the juvenile type of amaurotic familial idiocy, and (6) the Laurence-Moon-Biedl syndrome, in association with obesity, polydactyly, hypogenitalism and mental deterioration.

In addition to heredodegeneration, the neuroepithelium is also subject to heredoconstitutional diseases in the sense of Kehrler. These diseases are hereditary and familial but remain practically stationary throughout life. They are

1. Retinitis punctata albescens, in which the night blindness is practically stationary or very slowly progressive. The form of heredity is probably recessive.

2 Congenital night blindness without changes in the fundus. The condition remains unchanged throughout life. It is inherited in three forms: as a dominant (the Nougaret type), as a simple recessive and as a sex-linked recessive.

3 Oguchi's disease (congenital night blindness with grayish white discoloration of the fundus). The disease is familial, and its form of heredity is probably recessive. It remains stationary throughout life.

4 Color blindness

In addition to these heredodegenerations and heredoconstitutional diseases of the neuroepithelium, there are two diseases of unknown origin which stand in some relation to them:

1 Gyrate atrophy of the choroid and retina. There is no doubt that this disease is a familial heredodegeneration involving both the retina and the choroid. Which is the primary membrane involved is not known.

2 Choroideremia. This is probably a heredoconstitutional disease and has been observed in brothers. It is stationary throughout life, and other forms of heredodegeneration have been found in members of the families of reported patients. Mann stated the opinion that the sporadic cases of choroideremia are possibly purely developmental, the choriocapillaris having failed to form.

Ganglion Cells of the Retina—Heredodegeneration of the ganglion cells of the retina occurs in three distinct diseases, which also affect the ganglion cells in all parts of the central nervous system:

1 The infantile type of amaurotic familial idiocy (Tay-Sachs disease).

2 The juvenile type of amaurotic familial idiocy (Vogt-Spielmeyer or Stock-Spielmeyer or Batten-Mayou type). Included also is the late infantile type, which is, strictly speaking, an early juvenile type.

3 Niemann-Pick disease

The three diseases have in common a pathologic process which involves primarily the ganglion cells of the central nervous system, including those of the retina. The essential change is an accumulation of prelipids (sphingomyelin) in the ganglion cells, with eventual degeneration of the cells. The diseases are familial and hereditary, and it is possible that they are primarily heredoconstitutional instead of heredodegenerative.

They differ among themselves as follows:

1 In Tay-Sachs disease the ganglion cells of the central nervous system, including those of the retina, are affected.

2 In Niemann-Pick disease there is, in addition, an accumulation of foam cells filled with lipids in the liver, spleen, lymph nodes, thymus, adrenal glands, kidneys, stomach, intestine, pancreas and heart muscle

3 In the juvenile type of amaurotic familial idiocy there is, in addition to the changes in the ganglion cells of the retina and of the central nervous system, an associated degeneration of the extramacular neuroepithelium (retinitis pigmentosa)

Nuclear Layers—Degeneration of the nuclear layers, especially of the inner layer, occurs as a primary degeneration in the following conditions

1 As peripheral cystoid degeneration in senile, presenile and myopic eyes in the anterior portion of the retina near the ora serrata. It extends backward about 7 mm, rarely more. Its occurrence in presenile and senile eyes speaks for degeneration on a hereditary basis. In some eyes the cystoid degeneration is extensive and leads to rupture of the retina, to hole formation and to consequent retinal detachment

2 Retinitis circinata. Only a small number of cases of this condition have been studied histologically. In these a cystoid degeneration involved the nuclear and internuclear layers, with deposits of hyalin and fat and the presence of fat granule cells. The cystoid degeneration was particularly pronounced in the central area. The disease is not a common one and heredity studies are not available. However, such a disappearance of retinal elements, resulting in the formation of cystoid spaces, clearly indicates a primary degeneration and can only occur as a result of a hereditary defect

Nerve Fiber Layers of the Retina—There is no known heredodegeneration of the nerve fibers of the retina. But there is a disease of hereditary character affecting the central nervous system which also involves the nerve fiber layer of the retina, namely, tuberous sclerosis. This disease is difficult to classify. It is a heredodegenerative or heredo-constitutional disease and is also a congenital anomaly. It is a system disease in that it involves tissues over widespread areas in the body. Some investigators emphasize the neoplastic tendency of the tissues, others consider it the result of an early embryonic disturbance in organ formation. In the retina there occur in this disease tumors which seem to be derived from the nerve fiber layer and from glia cells in this and in the ganglion cell layers

SUMMARY

Under "heredodegeneration" are classified the diseases of the central nervous system which in the main are characterized by a specific loss of neural tissue as a result of hereditary influences. The term "abiotrophy" has essentially the same significance. By "heredo-

constitutional disease" is understood a disease which is the result of a hereditary vital defect in some tissue but in which there is no progressive loss of the tissue and the disease remains stationary for many years or throughout life

Such diseases occur in the retina and are found here under the following conditions

1 As a primary, separate and distinct disease of certain retinal elements Examples are retinitis pigmentosa and heredodegeneration of the macula

2 In association with another heredodegenerative disease of the retina An example is degeneration of the macula associated with degeneration of the neuroepithelium in the periphery

3 In association with hereditary diseases of the central nervous system Examples are degeneration of the macula associated with mental deterioration and retinitis pigmentosa in the Laurence-Moon-Biedl syndrome

4 As a part of a hereditary disease of the central nervous system An example is amaurotic familial idiocy

5 As a part of a widespread system disease involving many organs Examples are Niemann-Pick disease and tuberous sclerosis

The individual heredodegenerative diseases of the retina involve primarily certain retinal elements and can be classified as follows

A Originating in the elastic layer of Bruch's membrane

1 Disciform degeneration of the macula (Kuhnt-Junius type)

2 Angioid streaks in the fundus

(a) Occurring alone

(b) Occurring in association with pseudoxanthoma elasticum (Gronblad-Strandberg syndrome)

B Originating in the pigment epithelium

1 Hyaline or colloid bodies (drusen) of the basal layer of Bruch's membrane

C Originating in the neuroepithelium

I In the central, or macular, area

1 Heredodegeneration of the macula, including the infantile, juvenile, adult, presenile and senile types, occurring (a) alone or in association with (b) degeneration of the peripheral neuroepithelium, (c) atrophy of the optic nerve, (d) color blindness and (e) mental deterioration

II In the extramacular neuroepithelium

1 Retinitis pigmentosa, occurring (a) alone, or in association with (b) degeneration of the macula, (c) color blind-

ness, (*d*) deafness, (*e*) mental deterioration, (*f*) the juvenile type of amaurotic family idiocy and (*g*) the Laurence-Moon-Biedl syndrome

III Heredoconstitutional diseases of the neuroepithelium

- 1 Retinitis punctata albescens
- 2 Congenital night blindness without changes in the fundus
- 3 Congenital night blindness with grayish white discoloration of the fundus (Oguchi's disease)
- 4 Color blindness

IV Heredodegeneration of doubtful origin but standing in some relation to degeneration of the neuroepithelium

- 1 Gyrate atrophy of the choroid and retina
- 2 Choroideremia, a heredoconstitutional disease

D Originating in the ganglion cells

- 1 Infantile type of amaurotic familial idiocy (Tay-Sachs disease), affecting only the ganglion cells
- 2 Juvenile type of amaurotic familial idiocy, involving the neuroepithelium in addition to the ganglion cells
- 3 Niemann-Pick disease

E Involving the nuclear layers

- 1 Peripheral cystoid degeneration in senile and presenile eyes
- 2 Widespread cystoid degeneration, forming the basis for rupture of the retina with hole formation and consequent retinal detachment
- 3 Retinitis circinata

F Involving the nerve fiber layer

- 1 Tuberous sclerosis, a widespread heredodegenerative disease, causing the production of abnormal cells and tumors in this layer

ACTION SPECTRUM OF KERATITIS PRODUCED BY ULTRAVIOLET RADIATION

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KNOWLEDGE of the distribution of wavelengths and energies involved in the production of keratitis by ultraviolet radiation has theoretic and practical importance. Such information is fundamental to an understanding of the harmful photobiologic processes in the cornea and is prerequisite to the determination of exposure hazards and protective devices. The present report attempts to show quantitatively what bands of the ultraviolet portion of the spectrum are responsible for the production of keratitis and what relation the keratitis band has to the erythema band, to the characteristic absorption bands of some proteins and to the absorption of several types of common glass.

A curve relating wavelength to the quantity of energy just necessary to produce keratitis represents the action spectrum for keratitis, whereas a curve relating wavelength to the absorption of the corneal epithelium represents the absorption spectrum of the corneal epithelium. It is one aim of this study to correlate the action spectrum of keratitis with the absorption spectrum of a particular tissue constituent¹.

The action spectrum for keratitis has not previously been determined, although the long wavelength limit which would produce keratitis has been determined by use of filters, as in the standard work of Verhoeff and Bell².

PROCEDURE AND APPARATUS

The eyes of rabbits (albino) were exposed to separate bands of ultraviolet radiation at energy levels having a sufficient spread to determine the threshold dose necessary to produce keratitis³.

This study was supported in part by a grant made to the Howe Laboratory of Ophthalmology by the American Optical Company.

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

1 A subsequent report by one of us (V E K⁸) will show the characteristic absorption of various parts of the eye for the ultraviolet portion of the spectrum. The data in that paper will be drawn on freely where needed in the present report.

2 Verhoeff, F H, and Bell, L. The Pathological Effects of Radiant Energy on the Eye, Proc Am Acad Arts & Sciences 5 629-818, 1916.

The apparatus used was a Bausch and Lomb double monochromator (type no 33-86-05) containing two 8 by 8 cm quartz prisms, two quartz lenses and a high pressure General Electric mercury vapor lamp of 1,000 watt capacity⁴

The quantity of radiant energy was determined each day of experiment by means of a thermopile. This had been calibrated in absolute units of energy by exposing it to radiations emanating from a small opening of a furnace constructed in such a way as to possess all the characteristics of a black body radiator. The radiant flux measured in this manner is expressed in ergs per minute per square centimeter, from which the radiant energy, expressed in ergs per square centimeter, incident on the cornea is given by multiplying the radiant flux by the period of radiation employed. The measurements of energy are believed to have been determined with an accuracy of ± 25 per cent at the short end of the spectrum used and of ± 10 per cent at the long end.

The quality of the radiations was calculated from data supplied by Slaunwhite,⁵ in whose thesis is a detailed description of the method employed. All the exposures were carried out with entrance and exit slits set at 1 mm. With

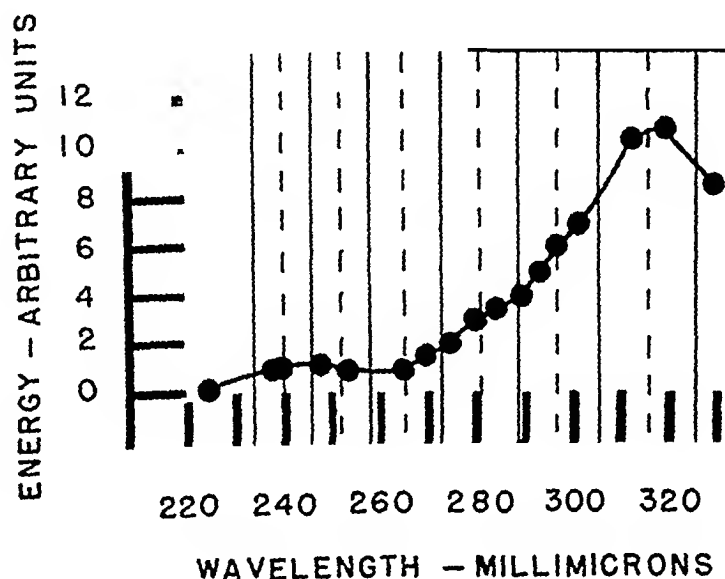


Chart 1—Distribution of energy at various settings of the monochromator. The settings are indicated by the broken perpendicular lines, whereas the total wave band for each setting is indicated by the blocked perpendicular lines.

these slit widths, the spectral region from 240 to 316 millimicrons was covered by six different bands approximately 20 millimicrons wide. To determine the peak sensitivity, two other bands, 280 to 296 millimicrons and 296 to 314 millimicrons, were used with the monochromator set at 288 and 305 millimicrons, respectively. With these two exceptions, the bands used are indicated by the

3 The energy necessary to produce keratitis with ultraviolet radiation in man has previously been determined to be approximately two-thirds that necessary in rabbits (Kinsey, V. E., Cogan, D. G., and Drinker, P. *Measuring Eye Flash from Arc Welding*, J. A. M. A. **123**:403-404 [Oct 16] 1943).

4 Loaned by Dr. J. R. Loofborrow and Prof. Francis Schmitt, of the Department of Biology at the Massachusetts Institute of Technology.

5 Slaunwhite, W. R. Jr. *An Investigation of the Rise of Monochromatic Ultraviolet Radiation in the Preparation of Vaccines*, Thesis, Massachusetts Institute of Technology, Department of Biology and Public Health, 1942.

blocked perpendicular lines in figure 1, and the monochromator settings, by broken lines

The absorption measurements for the glass filters and protein solutions were made with the Beckman spectrophotometer⁶ The nuclear protein used was prepared by extracting corneal epithelium with water and precipitating with 33 per cent ammonium sulfate The serum used was simply diluted with water

The dose was varied by controlling the duration of exposure, it being well established that these photobiologic processes obey the law of reciprocity⁷

During the exposure the rabbits were held immobile in a box, with head protruding through the end The lids were held apart manually and the eyes exposed for the desired length of time with the beam incident on the center of the cornea General anesthesia (pentobarbital) was rarely necessary, and then only with the extremely long exposures used in the experiments in which glass filters were interposed between the exit slit and the eye of the rabbit

The eyes were examined with the biomicroscope and slit lamp before the exposure and at successive intervals after the exposure of one day (eighteen hours) and two, four and seven days, or until the corneas had returned to normal

A total of 137 rabbit eyes were exposed Of these, the data on 9 are not recorded because of the development of corneal abrasions or other abnormalities which vitiated their inclusion in the series

The threshold dose was arrived at not only by determining the energy just necessary to produce an ocular reaction but by determining the transition between consistently negative and consistently positive results with increasing doses With rare exceptions, these two criteria were in agreement

GRADING OF OCULAR REACTION

The most reliable sign of keratitis with threshold reactions was, in our opinion a granular appearance within the corneal epithelium seen by transillumination with the slit lamp and biomicroscope The granules were of uniform size, each granule being of the order of size of a single epithelial cell The individual granules were round, but because of their small size no further details could be seen with a magnification of 40 With threshold reactions there were 50 to 200 of the individual granules, while with more severe reactions there was a corresponding increase in the number of granules, ultimately forming a mosaic Because of their size and uniformity and because of the occurrence of similar granules after irrigation with tap water, the granules are presumed to be swollen epithelial cells Histologic examination of corneas showing these minimal ocular reactions showed, with the usual fixatives and stains, nothing unusual

Associated with this granular appearance were a stippling of the surface of the cornea, seen in reflected light, and a varying amount of fluorescein "take" However, stippling is more difficult to assess quanti-

6 Loaned by Dr Theodore L Terry, of the Department of Pathology of the Massachusetts Eye and Ear Infirmary

7 Coblenz, W W, Stair, R, and Hogue, J M The Spectral Erythemic Reaction of the Untanned Human Skin to Ultra-Violet Light Radiation, Bureau of Standards J Research 8 541-547, 1932

tatively, and fluorescein "take" shows such a wide variation among normal rabbit eyes as to be misleading in the detection of minimal changes. Redness and discharge were even less reliable indexes. The criteria for evaluating the threshold reaction were therefore weighted heavily in favor of the granules.

With relatively severe exposures the corneal stroma became hazy. It is of interest that the cloudiness of the stroma occurred only with amounts of radiation which would be expected on the basis of transmission measurements⁸ to penetrate the cornea in sufficient quantities to produce a threshold reaction in the endothelium.

The ocular signs were maximal within the first two days after exposure, but their duration afforded a check on the reliability of the initial appearance. Only with severe exposures were residual signs to be found after seven days. During this time the granules disappeared, leaving an apparently normal cornea, in the case of threshold exposures, or one with varying degrees of optical irregularity and epithelial edema, in the case of suprathreshold exposures.

For tabular purposes, the ocular reaction was graded — to + + + +, according to the following arbitrary differentiation. Thus — indicated no abnormality, \pm indicated a probable but not definite abnormality, + indicated 50 to 200 granules with return to normal by the fourth day, + + indicated massive granules in the cornea for the first two days, optical irregularity on the fourth day and a return to normal by the seventh day with no cloudiness of the cornea at any time, + + + indicated massive granules during the first two days with mild cloudiness of the stroma, usually clearing by the seventh day, and + + + + indicated massive granular appearance during the first two days, considerable opacification of the stroma, loss of much of the epithelium and definite abnormalities still evident on and after the seventh day.

RESULTS

The ocular reactions produced by different energies at various wavelengths are represented in figure 2, with blocking of what we consider to be the threshold reactions. These threshold reactions are plotted in figure 3 to show the action spectrum or sensitivity at various wavelengths.

The significant features of the action spectrum are the shape of the curve, the point of maximal sensitivity and the long wavelength limit of reaction. The curve is obviously abrupt, with a peak at 288 millimicrons, and shows by extrapolation that the long wavelength limit lies somewhere between 306 and 326 millimicrons.

⁸ Kinsey, V. E. Spectral Transmission of the Eye to Ultraviolet Radiation, to be published.

Figure 3 represents the action spectrum for keratitis, the action spectrum for erythema (Coblentz, Stair and Hogue⁷) and the characteristic absorption spectrums of serum and nucleoprotein. The shapes of the

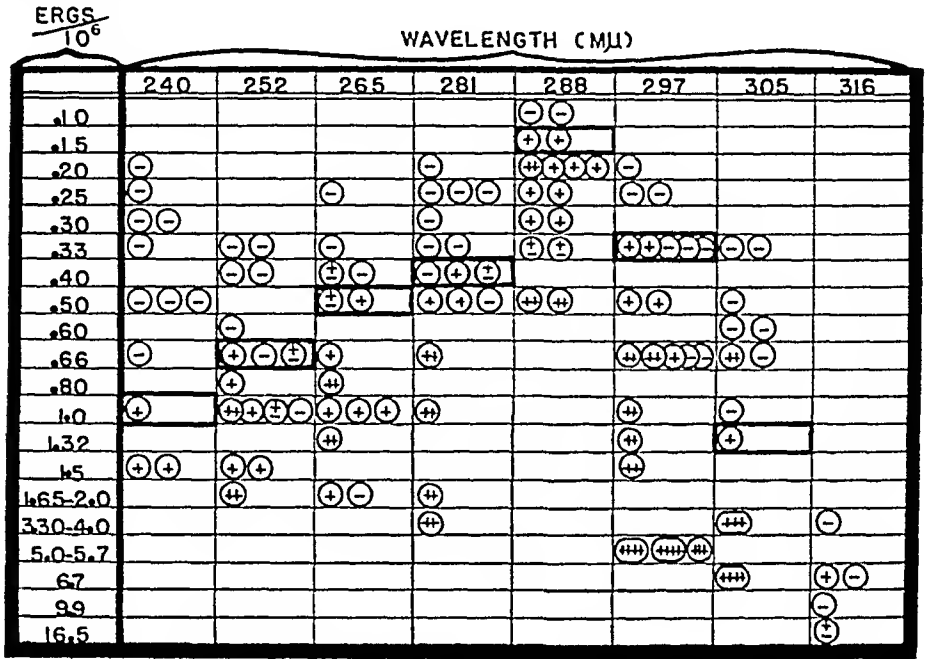


Chart 2—Reactions in rabbit corneas produced by exposure to bands of ultra-violet radiation of various wavelength at different energy levels. What are interpreted as threshold reactions are indicated by blocking.

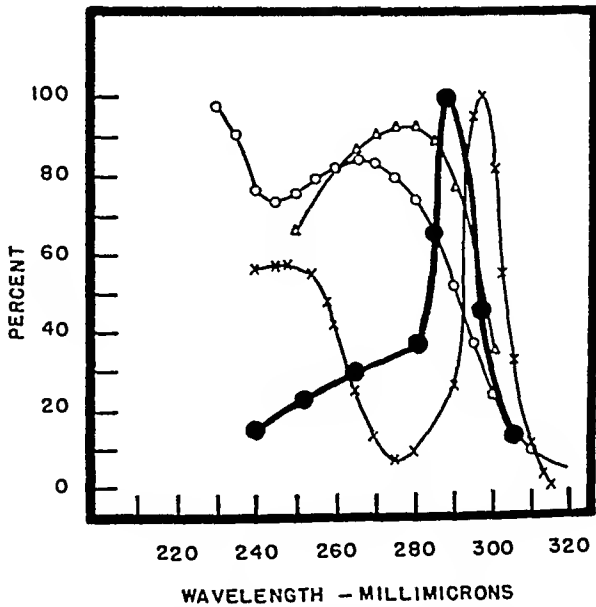


Chart 3—Curves illustrating the sensitivity of the cornea (line and solid dots) and of the skin (line and crosses) to bands of different wavelength and the characteristic absorption of nucleoprotein (line and hallow circles) and of serum protein (line and triangles).

keratitis and the erythema curve are similar, their difference lies chiefly in their maximums. The erythema peak is shifted more to the right than is the keratitis peak and both are somewhat to the right of the nucleoprotein peak. The keratitis peak most nearly coincides with the serum peak. The significance of these differences will be discussed subsequently.

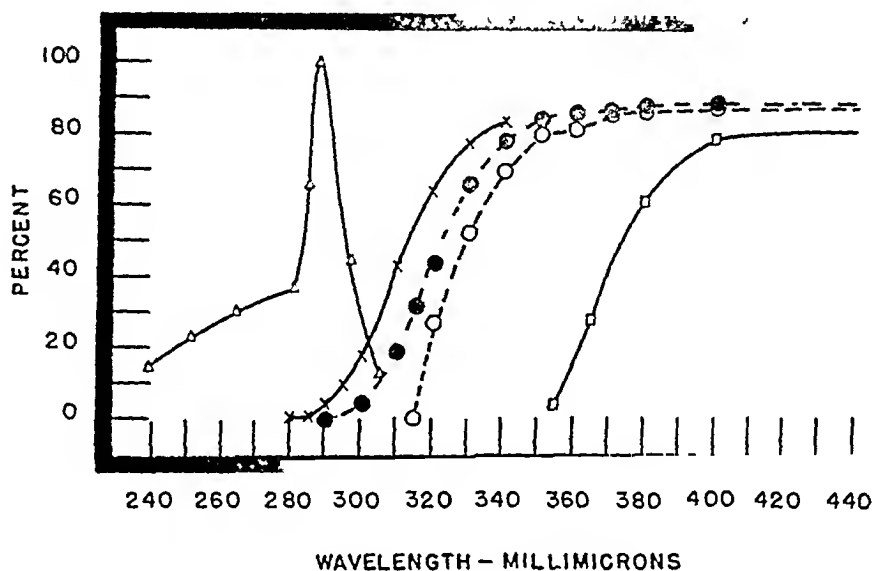


Chart 4—Curves illustrating the action spectrum of keratitis (line and triangles) and the absorption by glass of 2 mm thickness of the following types: crown or spectacle glass (line and crosses), window glass (line and dark circles), plate glass (line and hollow circles) and flint glass (line and rectangles).

ERGS 10^6	WAVELENGTH (Mμ)			
	288	297	305	
2.0		(-)		CROWN GLASS
2.5			(-)	
3.5	(-)	(-)	(-)	
5.0	(-)		(-)	
6.0		(-)		
7.5	(-)		(-)	
10.0		(-)		FLINT GLASS
15.0	(-±)	(+)	(+)	
103.0		(-)		

Chart 5—Reactions in rabbit corneas produced by exposure to bands of various wavelength when glass (2 mm thick) is interposed between the source of energy and the eye. The energies indicated are those which would be incident on the eye if no glass were used.

The energy necessary to elicit a threshold reaction in the cornea at the peak of sensitivity was of the order of 0.15 by 10^6 ergs. This is to be compared with the value of 2.0 by 10^6 ergs previously found⁹ when the whole ultraviolet portion of the spectrum was utilized.

⁹ Verhoeff and Bell.² Duke-Elder, W. S. Pathologic Action of Light upon the Eyes, *Lancet* 1: 1137-1140 (June 12) 1926.

The relation of the action spectrum of keratitis to the transmission of various types of common glass is represented in figure 4, and some experiments on rabbit eyes, using glass filters of 2 mm thickness, are presented in figure 5. In these experiments, the various types of glass were interposed between the exit slit of the monochromator and the rabbit eye. From figures 4 and 5 it is apparent that a 2 mm thickness of crown glass reduces the exposure hazard approximately fifteenfold at 305 millimicrons, forty-five fold at 297 millimicrons and a hundred fold at 268 millimicrons. A 2 mm thickness of flint glass affords essentially complete protection at all wavelengths.

COMMENT

The photosensitive substance in skin responsible for erythema after ultraviolet irradiation has been assumed to be protein in nature, and the lack of correspondence between the action spectrum of erythema and the absorption curve of the skin has been assumed to be due to the absorption and differential scattering effects of the superficial, inert layer of the skin. Thus, the interposition of a solution of "typical protein" in the path of the radiation results in a shift in energy transmitted, with a resultant curve similar to the erythema curve¹⁰. And, conversely, diminishing the scattering effect of the superficial layer by suitable clearing reagents results in an absorption curve for the whole epidermis similar to that for protein (serum albumin)¹¹. Presumably, therefore, if it were possible to eliminate the effect of the superficial, inert layer of the skin, the erythema curve would be shifted toward the shorter wavelengths, to have a peak sensitivity similar to that of protein at about 280 millimicrons. In the case of the skin, therefore, there is a reasonably good correlation between absorption by the epidermis and the erythema reaction.

The cornea has no superficial layer corresponding to that in the skin. It is interesting, therefore, to find that the peak of the action spectrum for keratitis corresponds approximately to that of the "corrected" erythema spectrum. But whereas the corrected erythema spectrum corresponded approximately to the corrected absorption curve for skin, both having peaks at about 280 millimicrons, the keratitis peak does not correspond to the absorption peak of the corneal epithelium, the keratitis peak is at 288 millimicrons, whereas the absorption peak of the corneal epithelium is at 265 millimicrons. Thus, while the values for the erythema spectrum are compatible with the assump-

10 Mitchell, J. S. The Origin of the Erythema Curve and the Pharmacological Action of Ultra-Violet Radiation, *Proc Roy Soc., London*, s B **126** 241-261 (Oct) 1938

11 Lucas, N. S. The Permeability of Human Epidermis to Ultra-Violet Irradiation, *Biochem J* **25** 57-70, 1931

tion that the ultraviolet radiation causes a general protein denaturation in the skin, since absorption and effect coincide, the values for the cornea indicate a selective effect at wavelengths other than those which are absorbed maximally by the cornea. The fact that the maximum absorption of the cornea occurs at 265 millimicrons suggests that nucleoprotein is chiefly responsible for the absorption, whereas keratitis occurs with a maximum that more nearly corresponds to that of the cytoplasmic proteins albumin and globulin.

From the absorption curve of corneal epithelium, there is no evidence of selective absorption at wavelengths corresponding to the peak of the action spectrum causing keratitis. This suggests that the amount of photosensitive substance present (albumin, globulin or other substance) is small, e g, an enzyme, or, alternatively, that the abiotic effects are due to absorption by some small fraction of the protein complex having absorption maximums similar to the keratitis maximum.

SUMMARY

The action spectrum for keratitis produced by radiation was determined on rabbit eyes. Relatively homogeneous radiations with sufficient energy to produce keratitis were obtained by means of a large quartz monochromator. The amount of energy at any one wavelength just necessary to produce a corneal change that was visible with the biomicroscope and slit lamp was considered the threshold dose for that wavelength.

The cornea was found to have a peak sensitivity to ultraviolet radiations at wavelengths of about 288 millimicrons, with a sharp decline in sensitivity to either side of the peak. The amount of energy necessary to elicit an ocular reaction at 288 millimicrons was approximately 0.15×10^6 ergs per square centimeter. Although the absorption peak of the corneal epithelium corresponded to that of nuclear protein (265 millimicrons), the peak of the action spectrum corresponded more nearly to the absorption peak of albumin and globulin (280 millimicrons). From this it may be inferred that the photochemical reaction in the cornea is due not to an indiscriminate absorption by nucleoprotein but, rather, to a selective absorption by a substance having a peak in the wavelengths longer than that of nucleoprotein or by certain constituents only of the nucleoprotein molecule.

The transmission characteristics of various types of common glass were measured for that portion of the spectrum which is responsible for keratitis. By comparison of these characteristics with the action spectrum for keratitis, it is possible to determine the amount of protection provided by any one glass for any wavelength or group of wavelengths.

INTRAORBITAL MELANOSIS AND INTRACRANIAL NEURO-EPITHELIOMA OF THE OPTIC NERVE

Report of a Case

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H. A. N., a 21 month old, irritable Armenian girl, was admitted to the service of Dr. A. B. Reese in the Institute of Ophthalmology in November 1943, with the history of an inflamed right eye for one month. The past history was irrelevant except for chickenpox at the age of 7 months and rubella at the age of 16 months. Examination, with the patient under ether anesthesia, showed a normal left eye. The right eye was enlarged and congested, with clear media, increased intraocular pressure (60 mm. Schiøtz) and extremely deep cupping of the optic nerve head (bottom of excavation seen with — 15 D. of the ophthalmoscope). In January 1944 iridencleisis with anterior sclerectomy was performed. Although the intraocular pressure became normal, the surgical procedure was followed by recurring intraocular hemorrhages, the development of a grayish white mass behind the lens and the loss of the reddish fundus reflex. The child acquired measles, and the right eye became more irritable. Enucleation of this eye was performed on June 2, 1944 by Dr. James McGraw. On removal of the globe, inspection of its posterior portion showed a ring of pigmented tissue around the entrance of the optic nerve. The orbit revealed an extension of this friable black tissue, which was dissected out. It seemed to extend about 1 inch (2.5 cm.) along the optic nerve posterior to the globe. A gold sphere was implanted into Tenon's capsule. Healing took place uneventfully.

On Nov. 22, 1944 the child was admitted to Babies Hospital in coma, after four days of vomiting. Physical examination showed elevation of the blood pressure (138 systolic and 110 diastolic), papilledema of the left eye, absence of the pupillary reflex, immobility of the left eyeball, trismus, absence of reflexes and flaccidity of all muscles of the extremities. Roentgenograms of the skull showed widened sagittal and coronal sutures, indicative of increased intracranial pressure. Blood cultures yielded no growth. A diagnosis of intracranial neoplasm was made. Supportive treatment was of no avail, and the patient died on November 23. The temperature, which was 100.6 F. on her admission, rose to 105.6 F. just before death. An autopsy was performed by Dr. Beryl Paige, who found no essential abnormalities except a tumor at the base of the brain.

This case was presented before the New York Academy of Medicine, Section of Ophthalmology, Jan. 15, 1945. An abstract of the paper was published in the April 1945 issue of the ARCHIVES, page 329.

From the Department of Pathology of the Institute of Ophthalmology of Presbyterian Hospital, and the Departments of Ophthalmology and Surgical Pathology of Columbia University College of Physicians and Surgeons.

REPORT OF PATHOLOGIC STUDIES

Right Eyeball (described by one of us [C A P])—Superiorly, the corneo-sclera showed an interruption of its continuity, and through the interruption extended pigmented, disorganized and atrophic iris tissue. The cornea superiorly revealed a dense fibrous membrane on its posterior surface, extending 2 mm from the limbus and reaching the curled-up end of Descemet's membrane. The anterior chamber was almost completely abolished except for a small portion inferiorly, the lens being pressed against the cornea. The ciliary body and the iris showed extensive degenerative changes, with dispersal of pigment. Extending

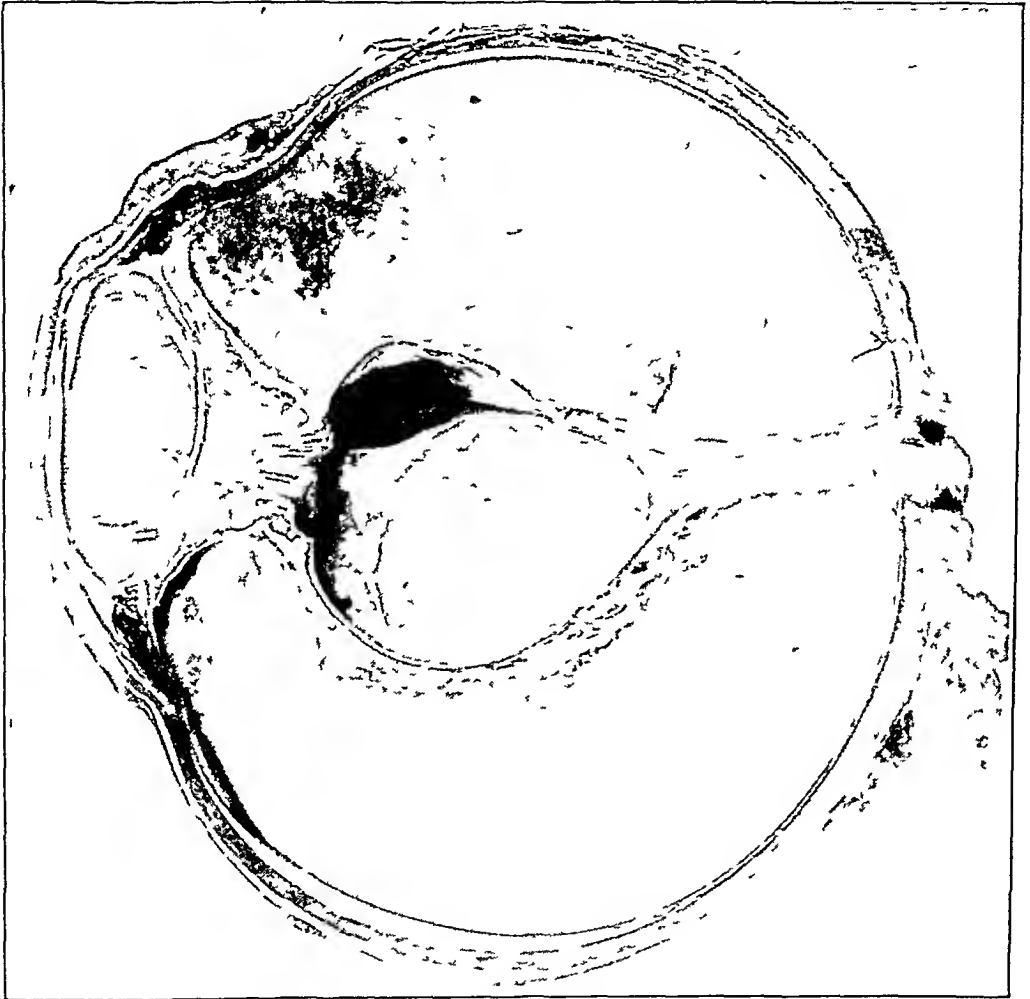


Fig 1—Low power photomicrograph of a cross section of the right eyeball, showing absence of the anterior chamber, fibrous membrane behind the lens, complete detachment of the retina and pigmented tissue around the optic nerve

across the eye behind the lens was a dense connective tissue membrane, to which the lens was adherent and into which was pulled the completely detached retina (fig 1). Immediately behind this fibrous membrane was a moderate amount of hemosiderin engulfed in phagocytes, as well as several large hemorrhages in the remains of the vitreous cavity. The subretinal fluid showed hemorrhage in its anterior portion. The choroid presented a moderate degree of pigmentation, and the lamina fusca contained a considerable number of chromatophores. At the posterior portion of the globe, the optic nerve had been pulled into the

interior of the eyeball by the dense retrolental membrane and the detached retina. The peripheral limits of the optic nerve sheath contained large numbers of chromatophores, which extended anteriorly to the level of the sclera (figs 2 and 3). Among the pigmented cells behind the globe were seen rounded hyaline bodies. Stains made with the Perl and the Turnbull method showed that the pigment in the optic nerve was not derived from blood pigment.



Fig 2—Detail of melanotic tissue bordering the optic nerve adjacent to the sclera

Tissue from Right Orbit (described by one of us [C A P])—The sections consisted of several small fragments of tissue from the orbit behind the globe. The significant features of these pieces were the extensive atrophy and gliosis of the optic nerve and the invasion of the periphery of this degenerated nerve tissue by pigment-containing cells, which formed an irregular layer around the optic nerve (fig 4). Internal to this layer of pigmented cells and interspersed

among them were seen many pale-staining, hyalin-like, rounded masses, some of which contained a small, endothelium-lined central lumen (fig 5) There were also a number of small, rounded, calcified concentrically laminated bodies (fig 6) The Perl and Turnbull stains showed that the brown pigment in these sections was not derived from blood Specific stains revealed that the rounded, hyaline

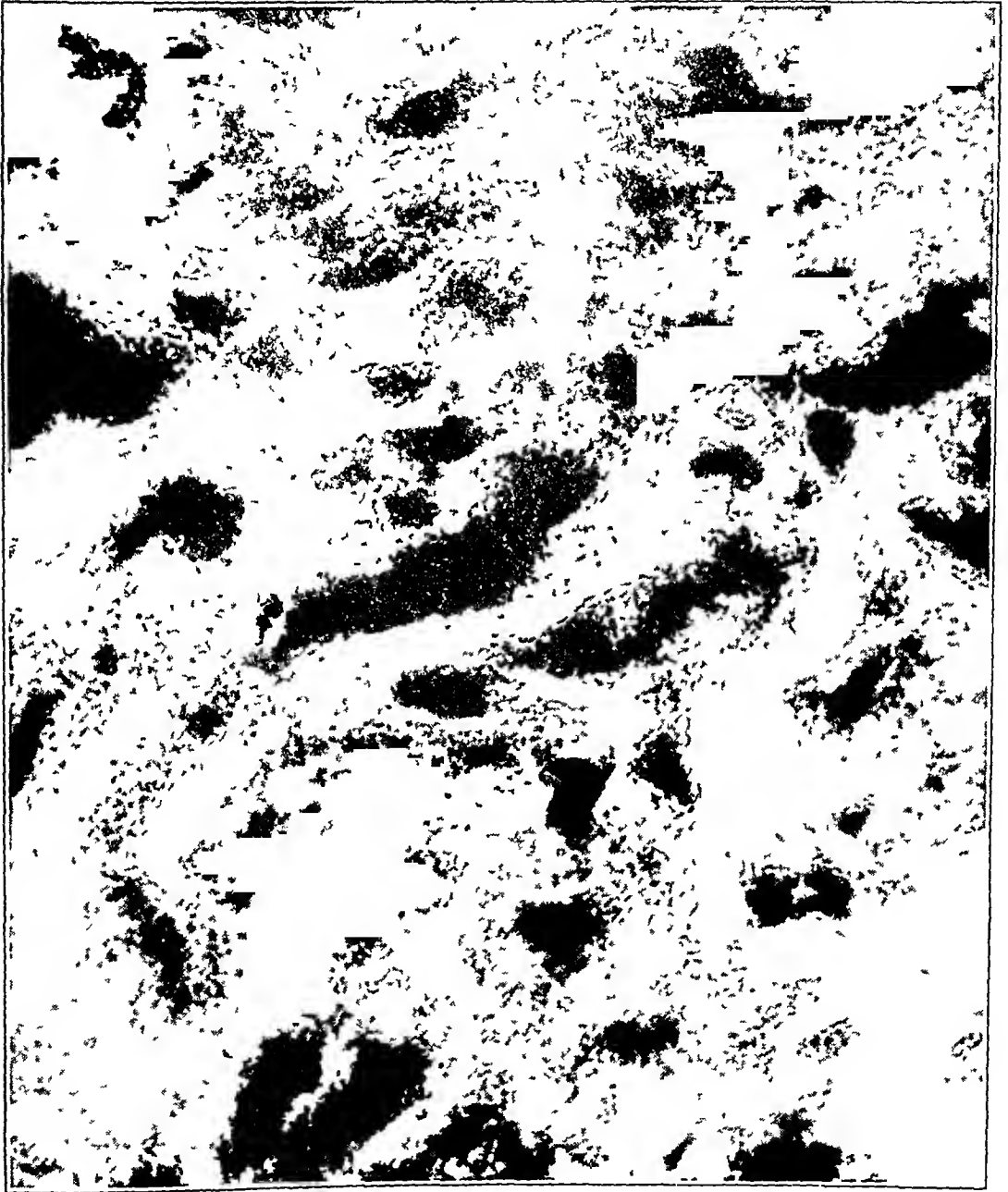


Fig 3—High power study of pigment-containing cells shown in figure 2

masses did not contain elastic tissue The degenerated optic nerve had a dense external dural coat

Conclusions from Pathologic Studies of the Eye—The globe was the seat of a previous glaucoma, for which iridencleisis was performed Subsequent to this operation there developed intraocular hemorrhages, with the formation of a dense connective tissue membrane behind the lens and complete detachment of the

retina. In the optic nerve behind the globe was seen an unusual pigmented lesion, associated with rounded, hyaline masses and small psammoma bodies. It appeared that the lesion of the optic nerve involved the arachnoid and pial layers of its sheath and that there was a melanosis associated with hyaline degeneration of the blood vessels of the arachnoid layer.

The pathologic diagnosis was hydrophthalmos, detachment of the retina following hemorrhage and contracture, melanosis of the optic nerve, iris inclusion operation.

Brain and Optic Nerves (described by Dr. Abner Wolf)—The cerebral hemispheres were approximately symmetric. They were enlarged and showed pronounced flattening of their gyri. In the midline at the base of the brain a tumor was found, diffusely infiltrating the hypothalamus, the optic chiasm, the lamina



Fig. 4—Low power photomicrograph of a cross section of the orbital portion of the right optic nerve, showing atrophic nerve fibers, surrounded by rounded hyaline bodies, pigmented cells and a dense dural sheath.

terminalis and the anterior extremity of the right optic tract. The right optic nerve was not separately visualized but was lost in the neoplasm. The left optic nerve was slightly swollen at its origin from the optic chiasm but appeared relatively normal anterior to that point. The tumor-infiltrated lamina terminalis was opaque and bulged forward as a large sac, approximately 17 cm in diameter, which compressed the posterior extremities of the gyri recti, the olfactory trigone, and the posterior third of the right olfactory tract. It extended asymmetrically to the right and elevated the anterior cerebral arteries. The tumor ended in the midhypothalamus. The remainder of the hypothalamus bulged and appeared somewhat hemorrhagic. On midsagittal section of the brain, the neoplasm described externally was found to extend through the hypothalamus into the

anterior two fifths of the third ventricle, partially obliterating it. It extended backward along the right lateral wall of the ventricle to the massa intermedia. The left lateral wall was the site of petechial hemorrhages. It appeared free from tumor. The rest of the ventricle was filled by a recent blood clot, with hemorrhagic tumor anteriorly. This had considerably dilated the cavity and obstructed the much enlarged interventricular foramina. The lateral ventricles were considerably dilated. The cerebellum and the brain stem showed no external abnormalities except for flattening of the dorsal surface of the cerebellum. The

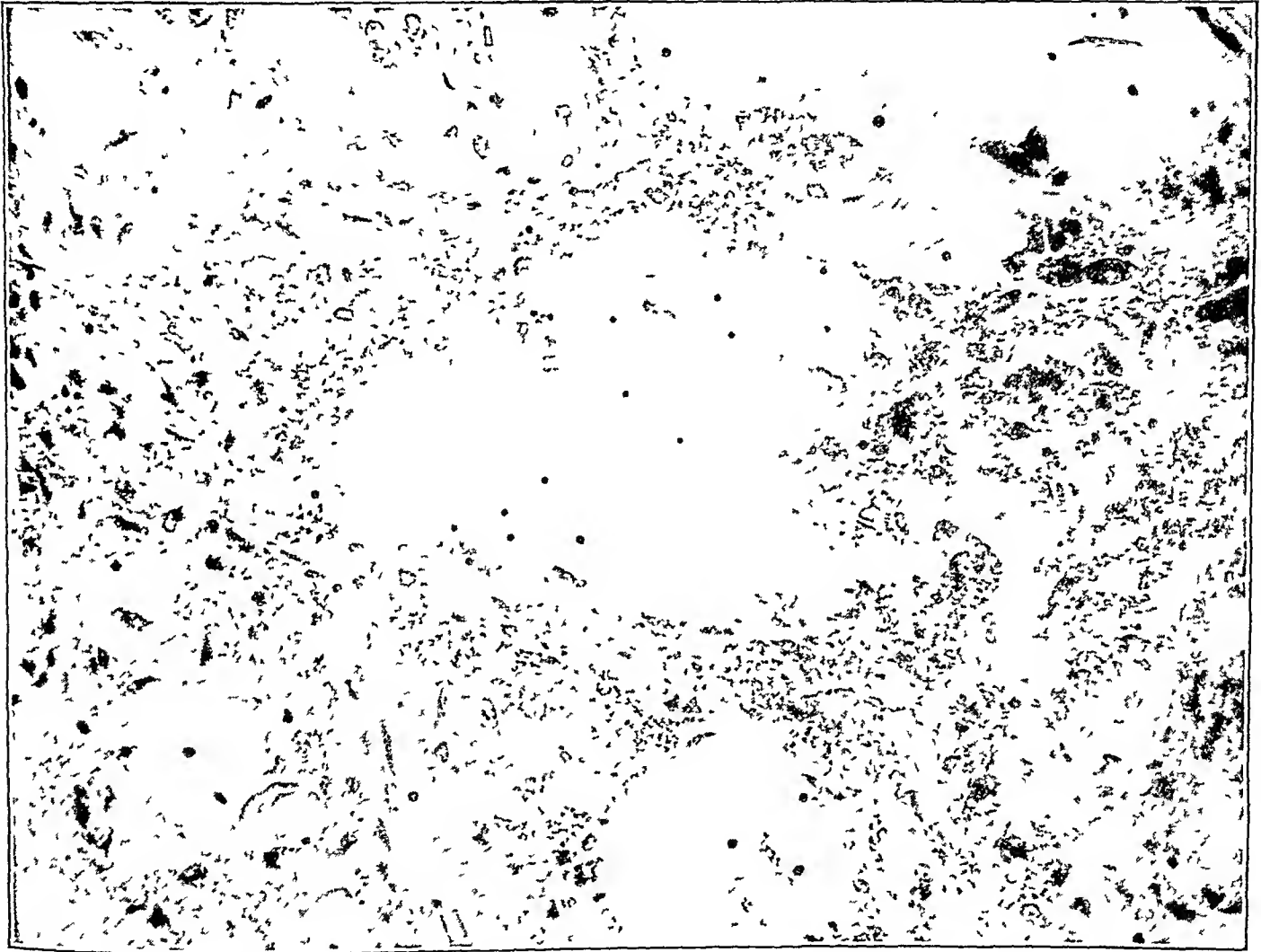


Fig 5—High power detail of figure 4, showing pigment-containing cells and adjacent hyaline masses

fourth ventricle appeared normal. Section of the cerebellum and brain stem revealed no gross abnormalities. The remainder of the right optic nerve was present in a separate specimen and was evidently the portion of the nerve in and anterior to the optic foramen, since it was already encased in its dural sheath. It appeared enlarged and centrally was occupied by grayish, slightly translucent tissue in an oval area, which compressed it for two fifths of its extent. Farther forward it was still larger, being approximately twice to two and one-half

times its size near the foramen. More than half the zone was occupied by gray, granular tissue, only a crescentic band of nerve remained grossly intact.

Microscopic study of the tumor showed that it consisted of small cells with dark-staining nuclei (fig 7), areas of calcification and occasional formation of typical rosettes (fig 8), especially in the tumor tissue present in the optic nerve.

The pathologic diagnosis was neuroepithelioma arising apparently from the right optic nerve or the optic chiasm.

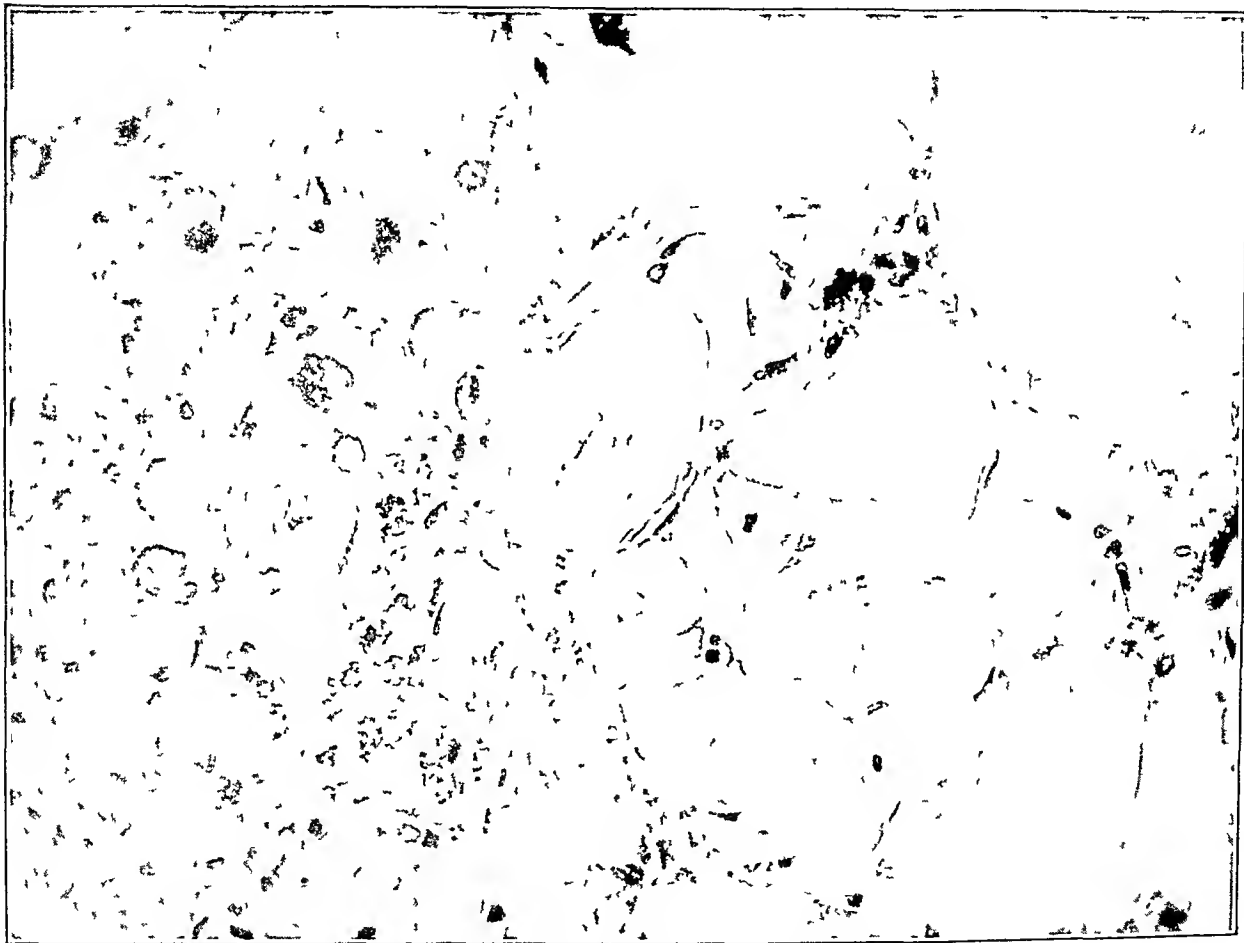


Fig 6—Another high power detail of figure 4, showing central endothelium-lined lumen of some of the hyaline structures and psammoma bodies.

COMMENT

An interpretation of this extraordinary case is difficult. The orbital melanosis of the optic nerve was distinct from the neuroepithelioma and arose in the sheath of the nerve. Perhaps the neuroepithelioma gave rise to some product which passed forward into the sheath of the right optic nerve and stimulated the production of the pigmented tumor.

The occurrence and distribution of melanotic cells in the leptomeninges have been carefully studied by Baader¹ Pigment-containing cells are found normally in the pia covering the optic nerves Excessive pigmentation (diffuse melanosis) of the leptomeninges of benign type and associated with multiple pigmented nevi of the skin has been described by Neubuerger, Daniels and Draper,² who cited 5 other

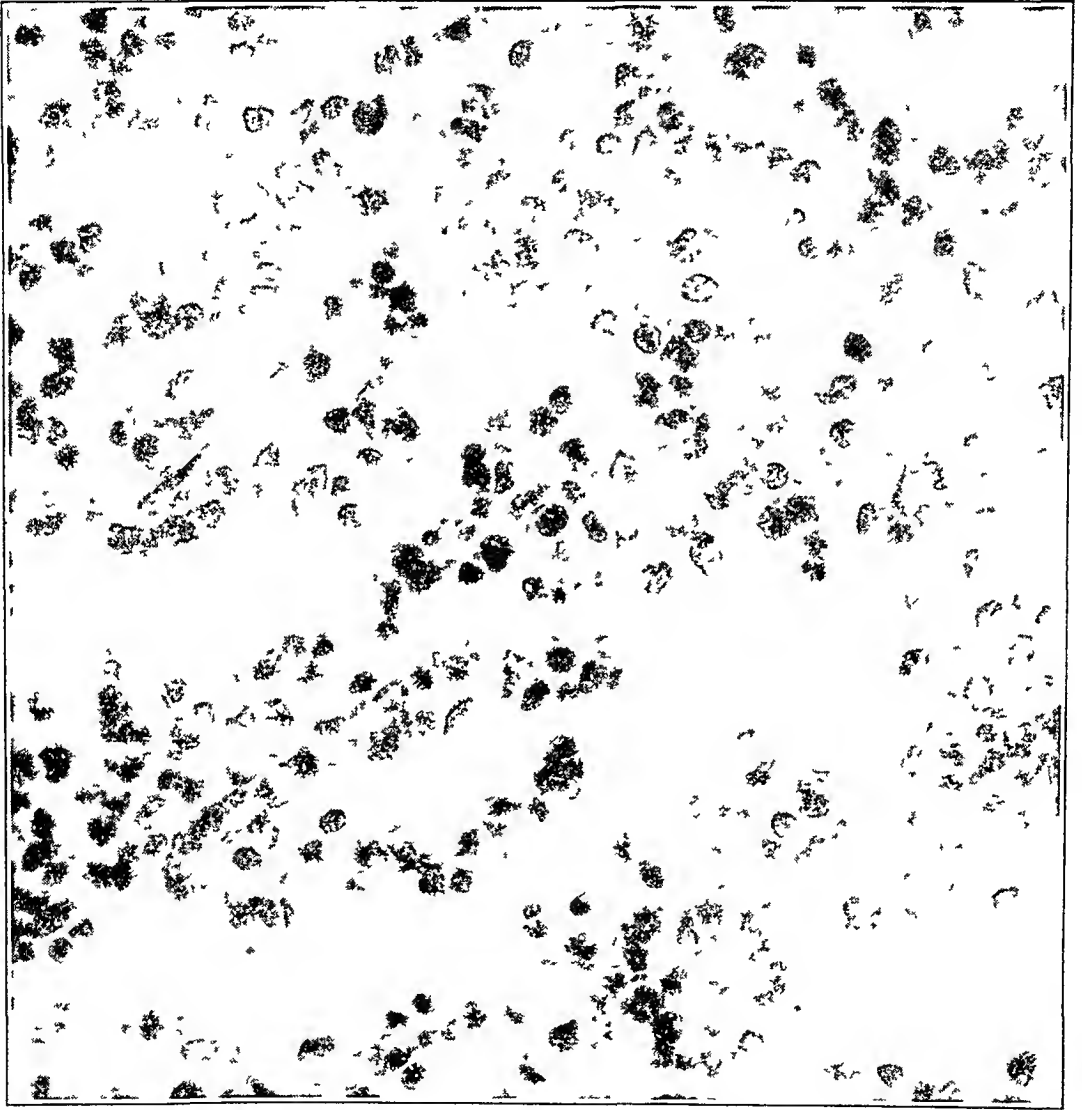


Fig 7—Photomicrograph showing appearance of cells of the tumor which infiltrate the base of the brain

authors reporting cases of the same association (Rokitansky, Netherton, Grahl, Wilcox and Bjoirnbøe) To these cases may be added 2

1 Baader, O Ueber die Piamelanose, *Ztschr f Zellforsch u mikr Anat* 22 735, 1935

2 Neubuerger, K T, Daniels, L E, and Draper, P A Nevocytoblastoma of Brain and Meningo-Cutaneous Melanomatosis, *J Neuropath & Exper Neurol* 2 140, 1943

similar cases reported by Christensen³ Rottino and Kelly⁴ described a case of malignant orbital melanoma and collected 43 other cases from the literature. If one can credit Theobald's⁵ hypothesis that melanomas of the choroid arise from the Schwann cells of the ciliary nerves, one might propose a similar origin from the Schwann cells of the orbital nerves for the intraorbital melanomas. A more recent case has been



Fig 8—Photomicrograph of a typical rosette found in the tumor of the right optic nerve adjacent to the chiasm

3 Christensen, E. Primary Intracranial Melanoma. Two Cases, *Acta chir Scandinau* 85 90, 1941

4 Rottino, A., and Kelly, A. S. Primary Orbital Melanoma. Case Report with Review of Literature, *Arch Ophth* 27 934 (May) 1942

5 Theobald, G. D. Neurogenic Origin of Choroidal Sarcoma, *Arch Ophth* 18 971 (Dec) 1937

reported by Foster⁶ A number of primary malignant melanomas of the leptomeninges have been recorded, and some of these have extended along the optic nerves (Farnell and Globus⁷, Schmitker and Ayer⁸)

Multiple malignant neoplasms of the eye and nervous system have been described Asbury and Vail⁹ reported a case of malignant melanoma of the choroid and glioblastoma multiforme of the cerebrum

Bailey and Bucy¹⁰ designated all the tumors arising in the meninges as meningioma with some qualifying adjective Consequently they spoke of a melanoblastic meningioma, but this is what others call a malignant melanoma The tumor in Cid's¹¹ case, arising apparently in the meninges of the restiform body, is unique, since it was made up of laminated fibrous elements resembling those of Darier's dermatofibroma and of melanoblasts Cid explained it as a nevoid melanoma which had arisen from pial melanoblasts and formed both schwannian structures and epithelioid melanoblasts

In view of the bizarre forms which melanotic growths of the meninges can assume, it seems to us wise to use the term "melanosis of the optic nerve" rather than "melanotic meningioma"

SUMMARY

We present the case of a 2 year old Armenian girl with glaucoma of the right eye, melanosis of the right optic nerve and neuroepithelioma of the right optic nerve, the optic chiasm and the base of the brain Complete pathologic studies of the involved tissues are reported The literature dealing with melanotic lesions of the leptomeninges is discussed

6 Foster, J Encapsulated Orbital Melanoma, *Brit J Ophth* **28** 293, 1944

7 Farnell, F J, and Globus, J H Primary Melanoblastosis of the Leptomeninges and Brain, *Arch Neurol & Psychiat* **25** 803 (April) 1931

8 Schmitker, M T, and Ayer, D Primary Melanomas of Leptomeninges: Clinicopathological Study with Review of Literature and Report of Additional Case, *J Nerv & Ment Dis* **87** 45, 1938

9 Asbury, M K, and Vail, D Multiple Primary Malignant Neoplasms Case of Malignant Melanoma of Choroid and Glioblastoma Multiforme of Right Cerebral Hemisphere, *Am J Ophth* **26** 688, 1943

10 Bailey, P, and Bucy, P C The Origin and Nature of Meningeal Tumors, *Am J Cancer* **15** 15, 1931

11 Cid, J M Meningioma neuronevo-melanoblastico *An de cir* **7** 137, 1941

Clinical Notes

USE OF PENICILLIN OINTMENT IN EXTERNAL OCULAR CONDITIONS

LEO L. MAYER, M.D., ST. LOUIS

ABOUT six months ago Eli Lilly and Company supplied me with $\frac{1}{8}$ ounce (3.8 Gm.) tubes of penicillin ointment for trial. The ointment contained 1,000 units per gram in the form of the calcium salt and, in addition, methiolate in 1:10,000 concentration. A caution on the label stated "New drug—limited by federal law to investigational use. Store below 10 degrees C (50 degrees F)."

This paper may be considered a preliminary report of observations on 100 patients at the time the ointment was prescribed, although for some conditions which failed to respond to the penicillin other medication was indicated.

Approximately one-half the patients were treated in the eye clinic of the Jewish Hospital. The patients and their conditions may be classified as follows:

Chronic conjunctivitis—no pus	10
Infected hordeolum	26
Infected chalazion	15
Acute nonpurulent conjunctivitis	21
Acute purulent conjunctivitis	28
	<hr/> 100

It should be stated that in cases of infected hordeolum and infected chalazion there was no attempt to incise or curet the abscess; instead, the penicillin ointment was used merely in external application.

The bacteriologic features of the infections were not made the subject of laboratory investigation, for two reasons: (a) By the time the majority of patients with conjunctivitis are seen by the physician, the infection having been present for many days, is of mixed type with one organism seldom predominating; (b) infection of the glands is notoriously of the staphylococcal variety.

The results of treatment were as follows:

1. No patient with chronic conjunctivitis received any benefit from the penicillin ointment, even after two to three months of treatment.

2. In all but 1 of the patients with an infected hordeolum the infection subsided in from three to four days. Also, it was not necessary, except in the case of the 1 patient, to incise and curet the abscess.

3. In every patient with chalazion the infection subsided in from four days to one week. However, it was necessary in 13 of the 15 patients to incise and curet the gland before the lid returned to normal.

4. In no patient with the nonpurulent type of acute conjunctivitis was there the usual response and cure of the condition in a seven day period, and in all cases other treatment was necessary after the use of penicillin in order to complete a cure.

5 In all but 2 of the 28 patients with acute purulent conjunctivitis a cure was effected in from three to five days. In the remaining 2 patients it was later discovered that, owing to a nasal condition, the nasolacrimal flow was blocked, with infection of the tear ducts. When this condition was remedied, there was prompt recovery from the acute purulent conjunctivitis with further use of penicillin.

It is to be noted that superficial infections of the skin around the lids cleared dramatically with simple application of the penicillin ointment to the surface of the skin.

A further investigation is contemplated in which a study of the offending bacteria will be made.

634 North Grand Boulevard

News and Notes

EDITED BY DR W L BENEDICT

SOCIETY NEWS

Central Illinois Society of Ophthalmology and Otolaryngology—The fourth meeting of the Central Illinois Society of Ophthalmology and Otolaryngology was held at the Hotel Orlando, Decatur, Ill., on April 27 and 28, 1946

The following papers were presented Saturday, April 27 "Perforating Ocular Injuries," Dr Perry E Duncan, "A Full Plastic Eye Implant" and "Exophthalmos," Dr A D Ruedemann, "Diagnosis and Treatment of Ménière's Disease" and "Selection of Cases for the Fenestration Operation in Otosclerosis," Dr Henry L Williams

Sunday, April 28 "Treatment of External Otitis," Dr Meredith Ostrom, "Headaches from the Standpoint of the Otolaryngologist," Dr H L Williams, "Treatment of Lesions of the Cornea," Dr A D Ruedemann

At the business meeting, at 1 p m on April 28, Dr Stuart Broadwell Jr was elected president for 1946, Dr Walter Stevenson, president elect, Dr Clarence E McClelland, vice president, and Dr William F Hubble, secretary-treasurer

GENERAL NEWS

American Orthoptic Council: Examinations for Technicians—The next examination by the American Orthoptic Council will be held in September and October 1946

The written examinations will be held at various cities in the country on Friday, September 6 Only those passing the written examinations will be permitted to take the oral and practical tests, to be given in Chicago, Saturday, October 12

Applications on official forms must be received before July 1, 1946

Address the American Orthoptic Council, 23 East Seventy-ninth Street, New York 21

Oxford Ophthalmological Congress—A meeting of the Oxford Ophthalmological Congress will be held at the department of human anatomy, Oxford University, July 4 to 6, 1946

Accommodation has been secured at Keble College, and the warden has kindly agreed to include lady members as residents in college Members will meet informally at supper on Wednesday, July 3, at 7 45 p m, in the Hall of Keble

The congress will open with a discussion on amblyopia, which will be led by Mr Philip Jameson-Evans and Mrs Dorothy Campbell

The Doyne Memorial Lecture will be delivered by Prof Arthur J Ballantyne and will be entitled "The State of the Retina in Diabetes Mellitus"

Facilities will be provided in the museum for demonstrations, and members are invited to bring forward cases, specimens, instruments, apparatus and other material of ophthalmologic interest

The council has decided that orthoptists shall be granted the privilege of attending the congress as visitors, on the invitation of a member, at sessions in which subjects affecting their department are to be discussed

Visitors may be introduced only if sponsored and paid for by a member, after formal application to the honorary secretary and after sanction has been granted by the council

The full program of the congress will be issued in June to all members in Great Britain and Ireland and to such members overseas as request it

Subscriptions should not be sent until the full program is received

Basic Course in Ophthalmology, The Post-Graduate School of the University of Southern California School of Medicine—The Post-Graduate School of the University of Southern California School of Medicine is presenting a six months' basic course in Ophthalmology, starting May 20, 1946 Dr A Ray Irvine, professor of ophthalmology, is director of the course, and he is assisted by Dr Maurice Beigelman, Dr William Endres and Dr S Rodman Irvine

The entire first month is devoted to preclinical courses organized by the following men anatomy, Dr Paul R Patek, physiology, Dr Douglas Drury, pathology, Dr Ernest Hall, bacteriology, Dr John F Kessel, pharmacology, Dr Clinton Thienes, biochemistry, Dr Harry Deuel Jr During the second month mornings are devoted to histopathology and afternoons to intensive work in physiologic optics The work of the third, fourth and fifth months stress clinical ophthalmology and refraction

Clinical instructors include Dr C H Albaugh, Dr Louis Bloomberg, Dr John Bullis, Dr Daniel B Esterly, Dr Channing Hale, Dr Deane C Hartman, Dr W C Irvine, Dr Raphael Koff, Dr George B Landegger, Dr John P Lordan, Dr Henry R Nesburn, Dr Robert A Norene, Dr M W Nugent, Dr Stephen Popovich, Dr Helen Preston, Dr Alfred R Robbins, Dr Carrol Weeks, Dr Clinton A Wilson, Dr Warren A Wilson, Miss Dorothy Franklin, Mr Russell Stimson and Miss Dorothy Bergin Dr Dwight Trowbridge, of Fresno, Calif, will be responsible for the section on neuro-ophthalmology

The sixth month will be spent in review, with emphasis on preparation for the examinations of the American Board Problem cases in refraction and therapeutics will be presented Several nationally known ophthalmologists, among them Dr Phillips Thygeson and Dr Meyer Wiener, will be available during this final month for short series of lectures

Examinations are to be given at the end of each month Sixteen students are enrolled, all being returned service men Enrolment was limited mainly by restricted facilities for work in refraction

Cooperation of the administrative and ophthalmologic staffs of the Los Angeles County Hospital is appreciated as essential for the success of the course

Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

General Diseases

OCULAR TUBERCULOSIS D LIVRAMENTO PRADO, *Arq brasil de oftal*
5 53 (April) 1942

Before presenting an interesting clinical observation on tuberculosis of the choroid and retina, the author summarizes the symptoms of this disease in the various parts of the eye, commenting on the many and varied treatments which produce results in specific cases. Treatment with tuberculin, gold, copper and chromium salts, and light, radium and roentgen rays is discussed. A detailed clinical observation is given, eight figures in black and white and two colored plates accompany the article.

M E ALVARO

OPHTHALMOSCOPIC EXAMINATION IN CASES OF ARTERIAL HYPERTENSION F AYRES, *Arq brasil de oftal* 7 95 (June) 1944

In his lengthy article, the author stresses the importance of an ophthalmoscopic examination in cases of arterial hypertension, pointing out that such an examination is often of the greatest value to the general practitioner. The two types of hypertension according to Volhard, (a) essential hypertension, red and solitary, and (b) pale, or malignant, hypertension, are discussed. The ophthalmoscopic pictures encountered, including discoloration of the arteries, central reflex from the vessels, changes in arterial caliber, alterations in the course of the vessels, the double white contour, exaggerated arterial pulsation and arteriovenous crossings, are described. Besides the vascular signs, retinal lesions, retinal hemorrhages, edema, white streaks and vascular retinopathies are dealt with in detail. Four figures and bibliography accompany the article.

M E ALVARO

Glaucoma

CONCEPT OF PREGLAUCOMA AND ITS DIAGNOSIS A MOREU, *Arch Soc oftal hispano-am* 4 313 (May-June) 1944

The author designates as a preglaucomatous eye one which is normal but on special examination exhibits some peculiarities. He makes this examination on all patients over 50 who consult him for vague visual disturbances, and he has been successful in averting the onset of glaucoma in 25 per cent of them.

The examination includes the following procedures: (1) biomicroscopic observation for changes in the small ciliary vessels near the limbus, (2) gonioscopic examination for pigmentary changes at the angle, (3) study of pupillary reactions, (4) observations on the

fundus, (5) determination of venous permeability of the eye, (6) study of the relationship of the retinal and the systemic blood pressure, (7) determination of the light threshold and studies of the light sense with the use of the adaptometer and campimeter

A detailed description of the procedure in all these examinations is given. The article is illustrated

H F CARRASQUILLO

Injuries

SEQUESTROMY IN GUNSHOT OSTEOMYELITIS OF THE ORBIT B RADZIKHOWSKY, *Vestnik oftal* 23: 34, 1944

In the material of the N ophthalmic evacuation hospital, osteomyelitis was observed in 20 per cent of cases of gunshot injuries of the bones of the orbit. Sequestromy was performed in 31 cases of injuries of the orbit, in 20 of these cases the lateral wall, in 4 cases the upper wall and in 7 cases the lower wall of the orbit was injured.

Radzikhowsky believed that sequestromy is the method of choice for treatment of osteomyelitis due to gunshot injury. The operation should be performed after the acute inflammatory symptoms disappear, i e, not earlier than six weeks after the injury. Both the sequesters and the necrotic parts of the bone should be removed. Any fistula which does not heal after a prolonged period should be carefully examined for sequesters. The rhinologist's assistance is valuable in cases of injury of the lower or the upper wall of the orbit.

In cases in which injury of the cranial bones is suspected the operation should be performed by a neurosurgeon.

O SITCHEVSKA

Lacrimal Apparatus

DACRYOCYSTITIS OF PEACETIME AND WARTIME V P STRAKHOV, *Vestnik oftal* 23: 4, 1944

Strakhov believes that both dacryocystorhinostomy and extirpation of the sac should retain their place. He gives a number of contraindications to dacryocystorhinostomy, in cases of which extirpation of the sac is indicated instead. Epiphora in wartime is frequently due to injury of the lids at the inner angle, and the greatest care should be taken in uniting perfectly the margins of the canaliculi.

During 1942 and 1943 101 operations for dacryocystitis were performed in N evacuation hospital, in 70 per cent of these dacryocystorhinostomy and in 30 per cent extirpation of the sac was done. In some of the cases of traumatic origin it was difficult to find the sac because of the presence of thick scar tissue, in cases of deformity of the bone it was necessary to enlarge the bony passage into the nose. Extirpation of the sac was done in cases of diseased sinuses, of syphilis (2), of trachoma (1) and of fistula and phlegmon of the sac (2).

O SITCHEVSKA

Lens

TRAUMATIC LENTICONUS POSTERIOR E ROSEN *Brit J Ophth* 29: 370 (July) 1945

Rosen gives the data in 2 cases and recalls 1 other case of traumatic posterior lenticonus.

A man aged 23 received a penetrating injury to the left eye after an explosion. A nonmagnetic foreign body entered at the corneoscleral margin, leaving a calcium-like scar. The portion of the iris corresponding to the injured sector was atrophic, detached from its peripheral union and tremulous. There was adhesion of the iris to the anterior capsule in the same meridian. The path of the projectile could be followed through the thickness of the lens to the posterior capsule, where there was a dense, almost chalky white, deposit with a metallic luster. The entire posterior cortex seemed encrusted with small white, round, saltlike deposits. The posterior capsule seemed to bulge posteriorly. Similar formations were seen in the vitreous.

The second case was one of chalcosis lentis associated with posterior lenticonus. The posterior capsule bulged posteriorly, and the posterior capsule appeared to be "rolled up" on itself in two regions, much like glass leisen bodies in the anterior chamber.

W ZENTMAYER

Lids

REPORT OF FORTY-EIGHT CASES OF MARGINAL BLEPHARITIS TREATED WITH PENICILLIN. M E FLOREY, A M MCFARLAN and I MANN, *Brit J Ophth* 29. 333 (July) 1945

Forty-eight patients with blepharitis were treated with local application of penicillin ointment containing 600 to 800 units of penicillin per gram of base. *Staphylococcus aureus* was isolated from the lesions of 39 of 41 patients examined bacteriologically. Thirty-six of the patients applied their ointment regularly three or four times a day for as long as it was considered necessary (i e., three to ten weeks). Recovery took place in all these patients without removal of other foci of infection or any adjuvant treatment other than epilation of a few lashes. Bacteriologic observations were found to be closely associated with clinical signs, but the disappearance of *Staph aureus* from cultures of material from the lids was considered a better indication for cessation of treatment than clinical signs as it invariably succeeded clinical improvement. A follow-up study a year after treatment was discontinued revealed that two thirds of the patients reporting had remained free of recurrence without further treatment.

W ZENTMAYER

TWO RARE CASES OF HOMOPLASTIC SURGERY OF THE EYELIDS. N I SHIMKIN, *Brit J Ophth* 29. 363 (July) 1945

Shimkin reports 2 cases in which homoplastic surgical treatment of the eyelids was successful.

In the first case post-trachomatous trichiasis in a hemophilic youth was treated with a graft from the buccal mucous membrane of his father. The second case was one of ichthyosis ectropion in a baby of 13 months suffering from congenital generalized ichthyosis. All four lids were affected. The ectropion was successfully treated with whole skin grafts from the forearm of his mother. No case similar to the first one was found in the literature, but Elschnig reported a case similar to the second.

The article is illustrated.

W ZENTMAYER

Ocular Muscles

HETEROPHORIA AND NEUROSIS IN FLYING PERSONNEL H C BECCLE
and E H KITCHING, Brit J Ophth 29:125 (March) 1945

The functional nature of heterophoria, the variable presence of symptoms, the inconstant relationship of symptoms and signs and the presence of associated nervous symptoms and indications of emotional instability, all suggest the existence of important psychologic factors in heterophoria, calling for investigation. With this end in view, 57 successive cases of hyperphoria in flying personnel were studied, 50 of the men were suffering from a well defined psychologic illness—either anxiety hysteria or hysteria. The conclusion, however, was that the heterophoria, though often the most prominent presenting symptom, was only one manifestation of a generalized psychologic illness, which was itself the main and primary disability. The results suggest that a psychologic examination is an essential part of the investigation of ocular imbalance. Local treatment should not be started until the presence and degree of the psychoneurosis have been determined.

W ZENTMAYER

MONOCULAR PARALYSIS OF BOTH ELEVATOR MUSCLES J MALBRÁN,
Arch de oftal de Buenos Aires 19:392 (Oct) 1944

Unilateral paralysis of both elevator muscles of the eye is not exceptional. The author has seen several cases in a comparatively short period. Its detection, however, is not common among ophthalmologists, since the methods of diagnosis are not sufficiently emphasized.

The lesion producing such a paralysis may be peripheral, in the nerve fibers of the oculomotor nerve, central in the neighboring nuclei, or supranuclear, in the motor fibers before they reach the nuclei in the mesencephalon. The first two locations are chiefly of theoretic importance, the lesion being almost always supranuclear.

The author gives a detailed description of the function of the elevator muscles and stresses the point that knowledge of their action in the various directions of gaze will lead to diagnosis of their paralysis. When a supranuclear paralysis occurs, Bell's phenomenon persists. This sign, of great diagnostic value, is, however, not mentioned by most authorities.

The surgical treatment of the condition is given. The article is illustrated with diagnostic photographs from 7 cases.

H F CARRASQUILLO

Parasites

HYDATID CYST OF THE ORBIT DIAGNOSED AS SARCOMA M ARNAU
MAORAD, Arch Soc oftal hispano-am 4:387 (May-June) 1944

The author was called by an otorhinolaryngologist to assist in an exenteration of the right orbit of a girl 18 years of age supposedly suffering from a sarcoma of the orbit, which had also invaded the maxillary sinus. The condition had begun one and a half years before with dull, continuous pain deep in the orbit, slight protrusion of the globe and diplopia. Three months later the pain was worse, vision began to fail and the proptosis increased. At the time of operation the pain was intense, the exophthalmos was extreme and the cornea was

necrosed. There was also a large tumorfaction over the maxillary sinus. A diagnosis of sarcomatous tumor of the orbit was made.

Exenteration of the right orbit was undertaken. When the needle was inserted in the upper and inner angle of the orbit to infiltrate the tissues with the anesthetic, about 60 cc of a clear crystalline fluid was evacuated. The diagnosis of hydatid cyst was made and simple enucleation of the globe was performed.

The author recommends that whenever the etiologic diagnosis of unilateral exophthalmos has not been clearly established, an exploratory puncture should be made before an operation is undertaken. Photographs of the patient appear in the article.

H. F. CARRASQUILLO

The Pupil

ADIE'S SYNDROME. C. GARBINO and C. CASTILLES. *Arch de oftal de Buenos Aires* 19:199 (April-May) 1944.

The authors report a case of Adie's syndrome (encephalomyelopathy of unknown origin), the second to be recorded in Uruguay. The patient was a nervous woman aged 35. She suffered from asthma, and in the routine examination the syndrome was incidentally discovered. She showed tonic pupils and generalized loss of tendon reflexes. The bilaterality of the ocular symptom and the generalized loss of tendon reflexes were peculiarities of the case. The serologic reactions for syphilis were negative. After an exhaustive study of the literature, the authors discuss fully the etiopathology and the pathologic physiology of the syndrome. An extensive bibliography accompanies the article.

H. F. CARRASQUILLO

Retina and Optic Nerve

TIME FOR OPERATION FOR RETINAL DETACHMENT. H. ARRUGA. *Arch Soc oftal hispano-am* 4:205 (March-April) 1944.

With the use of diathermy in the treatment of retinal detachment it is not always necessary to operate immediately as was formerly taught by Gonin. When there is pronounced bullous separation of the retina diathermy is often unsuccessful. Preoperative treatment should be given to allow the retina to be replaced. In summary, Arruga states: Operate at once in cases in which the retina is close to the choroid at the level of the tears, in cases of disinsertion and in cases in which the condition remains stationary or is progressive and the macula, though not yet involved, is menaced. Postpone the operation in cases in which there is bullous separation at the site of the tears or in which the detachment is localized or increased when the anatomopathologic conditions do not justify it.

H. F. CARRASQUILLO

Tumors

DIAGNOSIS OF OCULAR TUMORS BY MEANS OF BOTELHO'S REACTION TO AQUEOUS HUMOR. H. POVOA and A. PAULO JR., *Rev brasil de oftal* 2:193 (June) 1944.

Povoa and Paulo Jr performed the Botelho test for cancer on several persons in three small groups. (1) patients with nonmalignant

disease of the eye (detachment of the retina, acute glaucoma, chorio-retinitis and sclerochoroiditis), (2) normal persons and (3) patients with malignant tumors of the eye. The diagnosis of malignant tumor was made from the results of biopsy in 1 case and without a biopsy in 3 cases. The Botelho test gave negative results in the aqueous humor of the patients with nonmalignant disease of the eye, as well as in the aqueous of normal persons. It gave positive results in all 4 cases of malignant ocular tumor. The results of histopathologic examination of the eyes after enucleation confirmed those of the Botelho test. This paper is a preliminary report. The authors point out the advisability of performing the test in all cases of tumors posterior to the crystalline lens which are not amenable to biopsy and which are suspected of being malignant.

W ZENTMAYER

Uvea

GLAUCOMA AND ESSENTIAL PROGRESSIVE ATROPHY OF THE IRIS H S SUGAR, *Am J Ophth* 28:744 (July) 1945

A case of progressive atrophy of the iris with increased intraocular pressure is reported. Endothelial involvement and increased density of the iris at the area toward which the pupil was drawn were observed. The presence of increased intraocular pressure was explained by the dense peripheral anterior synechias. No attempt is made at present to explain the cause of the atrophy of the iris.

W S REESE

Vision

INFLUENCE OF SELECTED SPECTRAL DISTRIBUTION ON THE GLARE EFFECT STUDIED BY MEANS OF DARK ADAPTATION E SIMONSON, S BLANKSTEIN AND E J CAREY, *Am J Ophth* 28:712 (July) 1945

In 3 trained subjects the dark adaptation of the cones proceeded faster after exposure to an illuminant (B) whose spectral range had a reduction at each end of the visible spectrum than after exposure to the usual frosted lamps (illuminant A). The difference was not significantly influenced by four levels of preadaptation brightness, by daily variations or by individual variations. Evidence is presented that only the speed of dark adaptation is changed, without essential change in the contour of the curves. In a significant majority of 32 untrained subjects, the dark adaptation of the cones was faster after exposure to lamp B, except the first readings at 10 millifoot candles where no significant difference after exposure to lamp A and exposure to lamp B was observed. The difference in dark adaptation for lamp A and lamp B was about the same in four groups of 8 subjects each grouped according to the individual speed of dark adaptation. The usefulness of dark adaptation experiments for the appraisal of the glare effect is discussed.

W S REESE

Therapeutics

PENICILLIN THERAPY IN OCULAR INFECTIONS J G BELLows, Am J Ophth 27 1206 (Nov) 1944

Bellows gives a summary and draws the following conclusions

"1 Penicillin reaches the ocular tissues without a few minutes after intravenous injection

"2 After a large dose of penicillin is administered intravenously, it appears in the ocular tissues listed in decreasing order of concentration as follows extraocular muscles, sclera, conjunctiva, blood, tears, chorioretinal layer, aqueous and vitreous humors, and cornea It has never been detected in the crystalline lens In this respect, the lens is similar to the cerebrospinal fluid, brain, and nerve tissues

"3 Local application of penicillin leads to a very high concentration of the drug in the tissues of the anterior segment of the globe

"4 The following four ointments, in which the penetrability of penicillin was tested, are listed in the order in which they are clinically recommended simple ointment, oil-in-water emulsion, and lubricating jelly The 'vanishing' stearate type of a base, in which penicillin seems to have the greatest power of corneal penetration, is not recommended because of its possible damage to the corneal epithelium However, it may be used on the skin of the lids

"5 Penicillin was found to be effective in the clinical treatment of acute and chronic infections of the lids, conjunctiva, and cornea produced by penicillin-sensitive organisms

"6 It was found ineffective in two cases of exudative choroiditis of undetermined origin and in one case of gonorrheal iridocyclitis

"7 Susceptible individuals may become hypersensitive to penicillin"

W S REESE

PENICILLIN IN THE TREATMENT OF PERFORATING OCULAR INJURIES AND IN UVEITIS, R G SCOBEE, Am J Ophth 28: 380 (April) 1945

Scobee concludes from experiments that only instillation of penicillin together with intravenous injection of the drug is at all satisfactory in controlling severe ocular infection He tried lavage of the anterior chamber, subconjunctival injection, use of eye drops and intravenous injection He believed that penicillin is a definite adjunct to the therapy of uveitis

W S REESE

PENETRATION OF PENICILLIN INTO THE EYE R E WRIGHT, and C H STUART-HARRIS, Brit J Ophth 29 428 (Aug) 1945

The authors emphasize that their observations are incomplete because work was interrupted by circumstances beyond their control It is felt, however, that observations on the human aqueous humor were of sufficient interest to record, particularly as they tended to support the results of von Sallmann and Meyer obtained with animals

The following summary is supplied

Observations designed to indicate the most effective method of introducing penicillin into the eye are recorded. Penicillin reached the aqueous humor after local use in the conjunctival sac or after intramuscular injection, but the concentrations attained are variable and often low. By the use of iontophoresis, higher intraocular concentration can be obtained, but the technic requires considerable care and attention.

W ZENTMAYER

PENICILLIN IN OPHTHALMOLOGY T G W PARRY, G C LASZLO and J L PENISTON, *Brit J Ophth* 29:479 (Sept) 1945

This study has been largely directed toward ascertaining the value of penicillin in self administration by patients in their own homes. Methods of application, the use of penicillin for more severe conditions and some points of laboratory technic are also recorded.

The application of cream seems to be so far the only method of outpatient treatment. A preparation of standard strength of 250 units per gram dispensed in a screw-capped applicator tube in small quantity is employed.

W ZENTMAYER

INDICATIONS FOR RETROBULBAR INJECTION OF ALCOHOL A PAULO FILHO and J DE ARRUDA, *Rev brasil de oftal* 2:37 (March) 1944

Paulo Filho and de Arruda have for several years successfully resorted to the retrobulbar injection of alcohol in the therapy of acute ocular pain accompanying absolute glaucoma and acute hypertensive uveitis, as well as for the control of acute ocular and orbital pain in cases of ophthalmic herpes zoster, interstitial keratitis and acute ocular hypertension due to post-traumatic hemorrhage into the anterior chamber. The treatment consists of a first injection of 1 cc of a 1 or 2 per cent solution of procaine hydrochloride and, two or three minutes later, and without removal of the injecting needle, a second injection of 1 cc of alcohol, either absolute or of 80 per cent strength.

W ZENTMAYER

Society Transactions

EDITED BY DR W L BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA SECTION ON OPHTHALMOLOGY

Warren S Reese, M D, *Chairman*

George F J Kelly, M D, *Secretary*

Oct 18, 1945

Neurofibromatosis Occurring in Three Consecutive Generations Report of a Case DR EDITH HARVEY (by invitation)

A girl 5 years of age was seen in the clinic, with a history of gradual protrusion and deviation downward of her left eyeball. She was a healthy, intelligent child. She had had none of the usual diseases of childhood except an occasional cold. A tonsillectomy had been performed the previous year.

Examination revealed exophthalmos of 3 mm, with the visual axis directed downward 30 degrees and temporally 5 degrees when the visual axis of the normal eye was directed straight forward. Ocular rotations were fairly good in all fields except that of the superior rectus muscle, in which there was definite limitation. Visual acuity was 20/30 in the normal eye and 1/200 in the exophthalmic eye, and there was a definite papilledema in the latter. She had café au lait spots over her chest and abdomen but no subcutaneous neurofibromas.

The blood count and the urine were normal, as were the serum calcium and phosphorus.

Roentgenographic studies of the orbit showed no involvement of the bone except slight enlargement of the optic foramen on the side of the defect. The sphenoidal ridges were normal, and the bones of the skull showed no abnormalities. There was no evidence of calcification. Roentgenographic studies of the sinuses showed a normal condition.

The patient was operated on by Dr E B Spaeth. A neurofibroma was found encircling the entire intraorbital portion of the optic nerve, from its exit from the eyeball to the optic foramen. The eyeball and the optic nerve up to the foramen were removed. The tumor, which was about 9 mm in diameter along the entire length of the nerve, seemed to end at the optic foramen, where the optic nerve was of normal size, and it is to be hoped that the tumor did not involve the intracranial portion of the nerve.

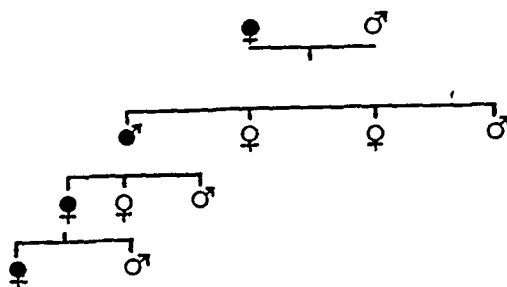
No other tumor masses were palpable in the orbit.

Microscopic sections of the enucleated eyeball and the nerve showed an intact, undamaged optic nerve, with a pure fibroma, containing no nerve fibers, surrounding it. There was, in addition, edematous infiltration of the nerve heads. (These sections will be discussed later in greater detail by Dr Perce DeLong, under whose direction they were made and carefully studied.)

The mother of the child has multiple cutaneous neurofibromas, most numerous over her back but scattered over her abdomen, neck and extremities. Many have been present since birth, others appeared at puberty. She has a few café au lait spots on her abdomen. Microscopic diagnosis of one of the tumors on her arm was neurofibroma. A similar tumor had been removed several years previously, and the same microscopic report was made.

The child's grandfather on the maternal side had died in Presbyterian Hospital. He had had a suboccipital craniotomy for neurofibromatosis involving the middle and posterior fossae. The diagnosis at autopsy was generalized neurofibromatosis, subserous neurofibroma of the stomach and a cervical perineural fibrosarcoma.

The antecedent relatives lived in Norway, and the only history obtainable was that the child's mother recalled hearing that her own grandmother, on the paternal side, had had several nodular masses on her face. Whether these were neurofibromas is of course impossible to determine.



Affected members in the direct relationship of the patient

The brother of the child and the sisters and brothers of the mother have no known abnormalities suggestive of neurofibromatosis.

Neurofibromatosis is a hereditary, and sometimes a familial, condition characterized by lesions of the skin and tumors on nerves. These lesions were discussed in detail. The author presented a brief résumé of the general symptoms.

The disease is congenital, showing mendelian dominance in successive generations, although occasionally a generation is skipped. There is no sign of sex-linked inheritance.

There seems to exist a congenital defect of the nerve sheath tissue, resulting in hyperplasia of the connective tissue of the nerve sheath, the cells being adult in type and not embryonic. The stimulus to hyperplasia is present from birth. New tumors may appear at puberty, during pregnancy or with intercurrent infections. They are not stimulated by local trauma.

The origin of these tumors has been a matter of controversy, which still is not settled. Von Recklinghausen expressed the belief that the tumors were mesoblastic in origin, arising from the endoneurium. Verocay stated that they were ectodermal, derived from the cells of the sheath of Schwann. According to Penfield and Young, they are the result of a reaction of connective tissue about the fibers of the nerves and show both nerve fibers and connective tissue elements, although the differentiated fibroblast, and not the glial cell, is the type cell.

Sarcomatous changes have frequently occurred in cases of neurofibromatosis. Operative removal of a neurofibroma may be followed by the recurrence of a benign neurofibroma. On the other hand, sarcomatous transformation may occur at the site of removal or in a distant preexisting nodule. Metastasis is relatively infrequent when a benign neurofibroma becomes sarcomatous, instead, such transformation is followed by transformation into sarcoma of a neurofibroma in another part of the body.

DISCUSSION

DR PERCE DELONG This syndrome is a disease of congenital origin characterized by cutaneous pigmentation and multiple tumors of cranial and peripheral nerves. The growths in Recklinghausen's disease are not true neuromas, which must consist of both nerve tissue and nerve cells, hence the term neurofibromatosis.

Penfield and Young, in describing the involvement of the nerve trunks, meninges and central nervous system, stated that there is a definite hyperplastic reaction of the cells peculiar to these tissues, indicating that an irritant or stimulating influence must have been exerted, causing hyperplasia, which was followed by true neoplastic growth of these cells.

This specimen does not differ from those described by other authors. The clinical ocular signs are secondary. These are exophthalmos, the result of pressure from behind, choked disk, due to pressure, degeneration, and atrophy of the optic nerve. Only van der Hoeve has reported involvement of the retina.

Pathologic examination in this case showed that the tunics of the globe were normal except for some edema of one ciliary nerve, with thickening of its sheaths. Then, too, there was early papilledema of the nerve head.

The optic nerve presents pronounced edema and definite fibrosis of the sheaths. Hyperplasia is most conspicuous in the region of the arachnoid, where the nerve has the appearance of being about twice its size. Microscopically no cellular elements are present, but pronounced hyperplasia and fibrosis of the nerve sheaths exist.

DR E. B. SPAETH I wish to call attention again to the development of sarcoma in cases of neurofibromatosis. I recently have seen 2 patients. The first was presented before this section about two years ago with neurofibromatosis in the upper division of the fifth nerve, and now sarcomatous changes accompanied with severe hemorrhages are present. The second patient had a neurogenic sarcoma that seemed to arise in an otherwise benign neurofibroma of the orbit.

The astonishing feature of the cases presented by Dr. Harvey is the great dissimilarity seen in 3 cases of a common hereditary condition. In the first case, that of the grandfather, there was a neurogenic sarcoma, i. e., sarcomatous changes associated with neurofibromatosis. In the second case, that of the mother, the lesions were confined entirely to the skin, and in the third case, that of the child, there was a neurofibroma of the optic nerve itself.

DR FRANCIS HEED ADLER I should like to ask Dr Harvey whether this tumor did not originate in the sheath of the nerve, rather than in the nerve fibers I should like to point out the error in the theory that neurofibromas start in the neurolemmal sheath, at least in the case of the optic nerve, because the optic nerve fibers, like the fiber tracts of the brain, have no neurolemmal sheath The optic nerve is not a true sensory nerve

DR EDITH HARVEY It is now generally believed that neurofibromas arise from the connective tissue sheaths of the nerves and not from the neurilemma, that is, they are mesodermal in origin

Early Ocular Pemphigus: Report of a Possible Case DR JOSEPH V KLAUDER (by invitation) and DR ALFRED COWAN

A white woman aged 29 since February 1944 had had recurring erosive areas on the buccal mucosa, the lips, under the tongue and on the floor of the mouth These areas disappeared and reappeared at intervals of from a few weeks to a few months When lesions appeared on the lips, she observed that the initial manifestation was a blister, which soon ruptured, leaving a crusted surface

In July 1945, when she was first seen, she had a cutaneous outbreak This was the first time such lesions had appeared On each elbow there was a bleb, which was partially collapsed The skin around the bleb was normal There was a similar lesion near the external canthus of the right eye The lower lip was covered with a crust, when the crust was removed a moist, bleeding surface was seen On the mucosa of each cheek there were margined, superficial ulcerations, the surfaces of which were covered with a yellowish membrane There were no vesicles on the lips or in the mouth

In August, during the time lesions were in the mouth and on the skin, both eyes became inflamed Examination showed intense infection of the palpebral and bulbar conjunctivas There was a distinct membrane on the tarsal conjunctiva of the lower lids and on the bulbar conjunctiva on the temporal side Both upper lids were similarly affected Biomicroscopic examination showed that both corneas were clear, there were no vesicles, the aqueous was clear, the iris intact and the lens unaffected

Infection of the conjunctiva gradually subsided, and the membrane on the conjunctiva of both eyes disappeared In the latter part of September there was a recurrence of conjunctival redness, with formation of a membrane on the upper and lower lids There was moderate swelling of the upper lid with free discharge No vesicles were seen in either cornea

The patient has had no fever and no constitutional symptoms Sulfadiazine was given internally, and sulfathiazole ointment was used in the eyes Solution of potassium arsenite U S P was administered by mouth in doses varying from 3 to 6 drops three times a day Repeated vaccinations for smallpox were performed A strict saltless diet was instituted

Ocular inflammation again subsided At the time of this report the patient presents only erosive areas on the inner surfaces of the lips and on the buccal mucosa

DISCUSSION

DR GEORGE J DUBLIN It has been my good fortune to be able to observe the course of the disease in this case from its incipience. When the patient was first seen, there was noted a severe inflammation of the conjunctiva. An extensive membrane was present on the tarsal conjunctiva of the lids. This membrane was yellowish, appeared to lie on the surface of the conjunctival epithelium and did not seem to involve the deeper layers. I tried to remove part of the membrane but was unsuccessful. Two or three days later a membrane was noted on the bulbar conjunctiva, both temporally and nasally, paralleling the limbal border, and in one eye it extended to the outer canthus. In addition, there was a profuse ropy discharge.

Dr Klauder's observation of a previous vesicular formation in the skin, together with stomatitis, pointed to possible pemphigus. Mild lotions were prescribed, and the condition cleared to a remarkable degree in seven to ten days, at which time the membrane had completely disappeared in both eyes.

The patient volunteered the information that as soon as the eyes would become well various sores would break out in the mouth. Her statement was correct. This condition in and about the mouth lasted four or five days, and then there was a recurrence of the ocular symptoms except that this time the membrane was even more extensive than in the previous flare-up. I have never seen a case in which there was such an extensive membrane formation. I did not know how to treat the condition, as there is no adequate treatment.

Other conditions simulating pemphigus are erythema multiforme, dermatitis herpetiformis and bullous syphilids. There are still other conditions which produce membranes, of the pseudo and the deep type of membranous conjunctivitis.

Membranous conjunctivitis involves the deep portion of the epithelium or the submucous portion and is considered invariably to be due to diphtheria. This patient was not acutely ill, nor was there any rise of temperature. As no diphtherial bacilli were found, the possibility of this disease was eliminated. Material for culture and smear was taken, but the bacteriologist was unable to identify the organism, stating that it was a rare gram-positive bacillus.

The patient had two other exacerbations associated with new lesions in the mouth. No special treatment was ordered, because it was thought that the condition would clear up under simple, bland medication. The patient, however, received sulfanilamide internally in doses of 60 grains daily (3.9 Gm) for approximately ten days. I do not feel that the disappearance of the membranes was due to the sulfanilamide therapy, because they had cleared up without it in previous attacks. I saw the patient about four days ago, when all the lesions and membranes had disappeared. It is significant that the cornea was at no time involved. There were no vesicles and no ulcers. In spite of the dense membrane which was present, the conjunctiva, both tarsal and bulbar, at no time showed any bleeding, ulcerated areas or areas of adhesion. Vision at all times was 20/20 in each eye.

Pemphigus is a rare disease. It may assume an acute or a chronic form. The acute form, occurring chiefly in butchers, is a virulent

disease, with severe constitutional symptoms, and frequently causes death. Chronic ocular pemphigus is frequently called essential shrinkage of the conjunctiva. The cause is unknown but the ocular condition is associated with bullae in the skin and mucous membranes in various parts of the body. In the eye, vesicles are rarely seen in the conjunctiva, in their place, small reddened areas are noted, probably the end result of broken bullae. This condition is frequently incorrectly diagnosed, or at least a proper diagnosis is not made until the late stages, when shrinkage of the conjunctiva takes place. This shrinkage is due to formation of connective tissue in the submucous portions of the conjunctiva, when this occurs, there is thickening of the conjunctiva with symblepharon and, eventually, ankyloblepharon.

Biomicroscopic examination in the late stages usually reveals perivascular thickening, together with a parchment-like appearance of the conjunctiva. Vesicles in the cornea are rarely seen, but corneal changes do occur secondary to the pathologic changes in the conjunctiva. The diagnosis is made generally by a dermatologist on the finding of bullae and vesicles in the skin and in the mucous membranes of the body, especially the mouth, larynx, nose and rectum. A pseudomembrane with a chronic type of conjunctivitis is sometimes seen. The membrane affects both the tarsal and the bulbar conjunctiva, in contrast to true pseudomembrane, which affects only the tarsal conjunctiva.

In the case presented by Dr Klauder and Dr Cowan there were noted vesicles in the skin and in the mucous membrane of the mouth, with a history of numerous exacerbations. The ocular changes consisted of membranous conjunctivitis, with numerous flare-ups and with complete disappearance of this membrane in seven to ten days. Although the conjunctiva has not shown any permanent defect, in all probability there will be alterations. Time alone will confirm or disprove the diagnosis of pemphigus in this case.

DR WILLIAM LAMOTTE, Wilmington, Del. Dr Klauder stated that there is no laboratory test for pemphigus. There is reported in the literature a so-called Macht test, with which I am not familiar, I wonder whether Dr Klauder would tell us what it is and whether it is of any value?

DR W E FRY. Another differential diagnosis at times may have to be considered, namely, the difference between vernal conjunctivitis and pemphigus. I mention this because of a patient who came under observation about a year and a half ago. The patient, a young woman was seen by Dr Klauder. She gave a history of multiple lesions of the gums, which necessitated the removal of all her teeth. Exactly what the lesions were is not known.

When I saw the patient, the ocular condition was that of papillomatous formation over the palpebral conjunctiva. The symptom of which she complained was intense itching. This led me to believe that the condition was vernal conjunctivitis. The smears showed an enormous number of eosinophils. There were numerous nodules, and microscopic examination of one of them showed that the tissue was similar to that of clinical vernal conjunctivitis.

Dr Klauder saw the patient and found evidence in the mucosa of previous lesions. He expressed the belief that the patient had pemphigus.

Since that time the patient has died. The exact cause of death I do not know except that it was not an accident, presumably Dr Klauder's diagnosis of pemphigus is correct.

DR WARREN S REESE I should like to ask Dr Klauder whether in his experience cutaneous lesions usually occur with ocular pemphigus.

DR JOSEPH V KLAUDER I do not think the Pels-Macht test is an infallible means of diagnosing pemphigus. False positive reactions are obtained, and I believe it is the consensus that the test is unreliable.

I cannot give offhand the percentage of cases of ocular pemphigus in which the disease exists without involvement of other mucous surfaces and without cutaneous lesions. It may occur without other lesions. It may accompany lesions of mucous membranes, and it may occur with lesions both of the mucous membranes and of the skin. I think, however, that in the minority of cases, I should guess in about 25 per cent, the disease is confined to the conjunctiva. In this connection, I cite Klauder and Cowan (*Am J Ophth* 25:643-661 [June] 1942).

Herpes Zoster Ophthalmicus Appearing After Trauma DR JOSEPH V KLAUDER (by invitation)

Report is made of 7 cases of herpes zoster appearing after injury to the skin or to the cornea, inflicted in various ways and of various degrees of severity. The disease appeared in the region of injury after an interval varying from one to nine days. In some of the cases symptoms of sensory disturbance or pain intervened between the injury and the outbreak of herpes zoster.

Of the 7 patients, 4 had herpes zoster ophthalmicus. The injuries preceding appearance of the disease were foreign body in the cornea, contact of the eye and forehead with sulfur dioxide and, in 2 cases, bumping one side of the head on a hard object without producing demonstrable injury to the skin.

Review of the literature disclosed many cases of herpes zoster appearing from one to thirty days after injury, at times trivial, to the skin or the cornea. Herpes zoster has also been reported as appearing after lumbar puncture, intramuscular injection of a medicament, osteopathic manipulation of the spine and high voltage roentgen radiation therapy in the region of a ganglion.

From the considerations discussed, it is reasonable that trauma may precipitate herpes zoster. The minimum degree of trauma and the interval between trauma and the appearance of herpes zoster necessary in order that trauma be ascribed a casual role cannot be precisely defined. Experimental evidence and clinical observation in cases of spontaneously occurring herpes zoster indicate that the incubation period of the disease ranges from a few days to about two weeks. In the cases of herpes zoster appearing after trauma which are reported here and in the cases recorded in the literature, an interval of one day to three weeks predominated.

DISCUSSION

DR WALTER I LILLIE Dr Klauder's presentation has interested me, inasmuch as in the cases I have reported concerning the use of smallpox vaccine in the treatment of herpes zoster ophthalmicus there has been no history of trauma. Because there has been such a tre-

mendous variation in the time of onset of the herpes after trauma in Dr Klauder's cases, varying from less than a day to six weeks, real doubt can be raised as to the importance of the trauma. As every one knows, it is not difficult to elicit a history of trauma in almost any case of any condition. I recall a patient I saw at the Mayo Clinic with one blind eye and a very small field of vision remaining in the other due to a tumor of the pituitary gland who received \$2,500 compensation when the court agreed with the patient that the visual loss was due to a pair of pliers striking his forehead. I am sure it is generally agreed that herpes zoster is a virus disease which has a definite period of incubation of a week or more and which belongs to the chickenpox family. This explains why cases of herpes zoster and of chickenpox may often be found in the same family. I should like to know what significance Dr Klauder places on the history of trauma in his cases.

DR GEORGE F J KELLY At present I have under my care a patient with herpes zoster ophthalmicus. According to her statement, five days previous to the appearance of the lesion hot lard splashed on the involved area. My feeling is that this was coincidental, and not causative.

DR JOSEPH V KLAUDER Experiments to ascertain whether herpes zoster is caused by a virus have given conflicting results. The opinion is stated by some investigators that the evidence is not conclusive and that herpes zoster may represent a syndrome resulting from any process causing inflammation of the spinal ganglion. Others accept experimental evidence as valid proof of virus causation and regard the elementary bodies demonstrable in vesicles of herpes zoster, particularly in the first forty-eight hours, as representing the specific virus of the disease. Proof of the virus causation of zoster is not so readily demonstrated as is such proof for herpes simplex.

DR WALTER I LILLIE It was my opinion that Filch, in his classification of ophthalmologic conditions, placed herpes zoster in the same large family with chickenpox.

DR JOSEPH V KLAUDER I am willing to do that, too.

DR WALTER I LILLIE The use of smallpox vaccine in treatment of herpes zoster was not original with me, but I have forgotten the name of the one who first used repeated injections of the vaccine.

DR JOSEPH V KLAUDER A virus causation of herpes zoster is the basis of this treatment.

DR JOSEPH V KLAUDER What about trauma as a factor?

DR WALTER I LILLIE From a review of the cases that I have had and the résumé of the literature by Edgerton I could find nothing correlating trauma with herpes zoster.

Surgical Methods of Treating Paralysis of the Superior Oblique Muscle DR WILLIAM E KREWSON, III

Isolated unilateral paralysis of the superior oblique muscle is frequently encountered, bilateral involvement, occasionally. The literature records relatively few cases of the condition treated surgically and in these reports a great variety of procedures is offered, most of the muscles of each eye have been used in one way or another at some time. These methods include weakening of the homolateral superior

rectus advancement of the homolateral inferior rectus advancement or transplantation of the homolateral external rectus weakening of the contralateral inferior rectus, tenotomy or recession of the homolateral inferior oblique, shortening of the contralateral superior rectus, advancement of the paralytic superior oblique muscle and various combinations of two or more of these operations.

No standard sequence of corrective measures can be advocated for all cases, the plan of attack must be based on measurements found in the individual case. If a choice is permitted weakening of a depressor muscle is undesirable, strengthening of a depressor or weakening of an elevator muscle is preferable. In cases of paralysis bilateral equalization and preservation of the remaining depressor muscles are advisable.

DISCUSSION

DR FRANCIS HEED ADLER I should like to discuss more fully a factor which occasionally leads to an erroneous diagnosis in cases of paralysis of the superior oblique muscle. The condition was first pointed out, I believe, by Chavasse, under the designation "inhibitional palsy of the contralateral antagonist." It is seen in cases in which fixation is customarily carried out by the eye with a paralyzed superior oblique muscle. In these cases not only is there a characteristic limitation of movement downward and to the side opposite that of the paralyzed superior oblique but there is also limitation of movement of the nonparalyzed eye on looking up to the ipsilateral side. For example, in a case of paralysis of the left superior oblique the left eye fails to move down when the eyes are turned down and to the right. In such a case the right eye fails to move up when the eyes are turned up and to the right. This condition may easily be mistaken for paralysis of the right superior rectus muscle. The explanation of this so-called inhibitional palsy, I believe is somewhat similar to the explanation of the vertical separation on looking down and to the right when the left superior oblique is paralyzed. The latter is due to two factors (1) the weakness in the left superior oblique muscle and (2) the overaction of the right inferior rectus muscle. This overaction is explained by the well known law of Hering namely, that all voluntary movements are brought about by equal innervation of the muscles of the two sides concerned in the movement. When one looks down and to the right, an equal innervation is sent to all the muscles of the two sides which carry the eyes in this direction. When one of these muscles is weak, the total amount of innervation is increased so as to bring about the full movement of this weak muscle, but the same amount of innervation is sent to the yoke muscle of the opposite side, and so this muscle "overacts."

When a patient with paralysis of the left superior oblique looks up and to the right with the left eye fixing, the movement in this direction is made easier by the paralysis of the left superior oblique, because the left inferior oblique now has no resistance from its opponent. Less energy will be required, therefore, to turn the left eye up and to the right, accordingly, less innervation is sent to the yoke muscle of the left inferior oblique, namely, the right superior rectus, and this eye fails to move up as far as the left. Slides of 2 cases were presented.

DR GLEN G GIBSON Dr Krewson has covered the subject completely, and the paper is a timely one. I was interested in this pre-

sentation because of the experiences which I have had in cases of mistaken palsy of the superior oblique muscle. One of the common conditions which may be incorrectly diagnosed is that which simulates convergent strabismus. In cases of such palsy the strabismus begins primarily as a paralysis of the superior oblique, but as time goes on it becomes concomitant. Such a condition is impossible to differentiate from the usual accommodative convergent strabismus. In cases of this type I have at first failed to recognize the origin of the condition in the vertical muscles and have operated as though the squint was of convergent type, only to have the patient return with an unsatisfactory result and then, on further study, to find that the paralysis was of trochlear origin. A second operation then had a gratifying result, the surgical procedure having been done in accordance with the primary pathologic condition.

Careful attention to the sensory correspondence is helpful in selecting the proper type of operation and the amount of surgical correction. This is simply illustrated by a case of traumatic trochlear palsy of one year's duration in which there was 21 prism diopters of hyperphoria. The patient was subjected to recession of the inferior rectus muscle of the unaffected eye. After the operation, which consisted of a 2 mm recession of the inferior rectus, there was no hyperphoria. In other words, the 21 prism diopters of hyperphoria had been reduced to zero by a minimal recession. The important point in this case is not that a precise measurement of the amount of necessary surgical correction was made but, rather, that a good surgical result was achieved because this patient originally had, and always maintained, normal binocular vision until his accident. I needed only to put the eye approximately in its normal place. The sensory mechanism came to my assistance and brought the eyes to the exact place that was wanted not because the surgical correction was precisely accurate but because normal binocular vision was present before the accident.

In cases of long standing or of congenital hypertropia a recession of 2 mm is inadequate to bring about the desired result, particularly in cases of pronounced vertical hypertropia, and in such cases it is necessary to do as much as 4 or 5 mm of recession, and that is about the maximum amount of recession of the inferior rectus muscle of the other eye which one should do. In some cases of long standing hypertropia, particularly in adults, it is necessary to combine the recession of the inferior rectus of one eye with a tenotomy of the inferior oblique of the paralytic eye.

Another important point is the recognition of birth trauma and heredity as causative factors in trochlear paralysis. As an illustration of the hereditary factor, I recently saw two grandmothers of 2 patients on whom I had operated for trochlear paralysis. They had had the same condition all their lives. Birth trauma is a common cause, and it is fruitful to inquire particularly regarding forceps delivery as a possible cause of trochlear palsy. It is also important to consider the degree of binocular vision which the patient has. If the condition has been present from birth, the patient never had binocular vision except in abnormal positions of the head, and a much more extensive surgical procedure has to be done than in a case of traumatic origin.

Book Reviews

Eléments de gonioscopie normale, pathologique et expérimentale
By Archimede Busacca, São Paulo, Brasil Tipografia Rosohillo,
1945 Pp 201, with 107 illustrations (1 color plate)

Dr Busacca is a distinguished Italian ophthalmologist and investigator who emigrated to Brazil some years ago and lately has undertaken the study of gonioscopy. This book is a valuable addition to the literature of this fast growing department of ophthalmology. Dr Busacca has made his examinations of the angle of the anterior chamber with the Goldman contact glass, which permits observation with the patient sitting up in front of the observer, as in ordinary slit lamp microscopy. The image of the angle is seen not directly, as with the gonioscope, but indirectly, in the depth of a plane mirror. Also, the two sides of the angle appear somewhat foreshortened. The Goldman glass permits a comparatively easy observation of the upper and lower parts of the angle, but the temporal and nasal sides are difficult to illuminate and bring to focus properly. To avoid this drawback, Goldman has devised a special reduction prism which is attached to the arm of the biomicroscope.

Dr Busacca's book is primarily the work of a histologist who applies his microscopic knowledge to the study of gonioscopy. He used especially the narrow slit of the biomicroscope in optical section to determine the arrangement of the structures in depth, and he thinks that a strong light is confusing and dazzling to the observer. He asserts that, although using better instruments, modern authors "have not added anything to the observations of Salzmann with the ophthalmoscope" and "entirely ignore structural details which this author pointed out."

This assertion is not accurate. Probably Dr Busacca has studied the angle particularly in the articles of former observers, such as Virchow, for the histologic characteristics, and Salzmann, for clinical details. He entirely ignores the work of modern authors, for instance, he dismisses with two or three words all the research on comparative anatomy of the angle which I have published and which throws great light on the architectural building of the structures of the chamber recess.

The first part of his book is devoted to the histology of the angle. Although he criticizes the authors who have "a mania for creating new names," he immediately proceeds to give new ones to almost all the organs and tissues seen in the gonioscopic field. Starting with the Schwalbe line, which he calls the "anterior limiting white line," and the scleral spur, which he calls the "white line of the spur," he describes the band of the ciliary body as "the shadow of the muscle." This entirely inappropriate name is meant to convey to the observer the fact that the fibers of the ciliary muscle are present behind the surface of the ciliary body. He asserts that the "shadow" of the circular bundles of the muscle can be seen with a narrow slit. To increase the confusion, he divides the "muscular shadow" in two bands, which are of different color, the anterior band, near the spur, is of a darker gray

hue, and he calls it "the suprachoroidal shadow." This color is determined, in his opinion, by the pigment present at this place on the inner surface of the sclera and between the longitudinal fibers of the muscle. The posterior band is a lighter brown. He believes that the muscle fibers are "probably" red, although it is known that smooth muscles are usually gray white.

Studying the iris, he describes cases in which the most prominent ridge in the membrane, instead of being near and over the sinus of the chamber, is placed a little forward on the surface of the iris. He gives the name "iris groove" to the part of the surface of the iris behind the most prominent ridge. The designation is inaccurate, as there is no groove at this place—only the flat surface of the iris, which runs directly outward, to attach itself to the anterior surface of the ciliary body.

He calls the "basal band of the iris processes" the part of the root of the iris to which are inserted the so-called iris processes. I have shown conclusively by studies in comparative anatomy that these "iris processes" are the rudimentary fibers of the pectinate ligament, so strongly developed in lower mammals. These fibers have also been described as the "uveal trabecula." Busacca gives them three different names. Sometimes he calls them "iris processes", at other times the "uveal trabecula" and at still others the "iris trabecula." In his color scheme of the structures of the angle, he shows the pectinate fibers as arising from almost one third of the peripheral surface of the iris. This is contrary to all my microanatomic observations. It appears that he made this drawing partly from anatomic specimens. He probably stretched the iris so much that the root became longer and the pectinate fibers advanced forward.

An anatomic characteristic described by Busacca is worth while retaining. The band of the ciliary body is covered with a semitranslucent membrane, which he calls the "trabeculoconnective lamella." This is made by the lower portion of the corneal trabecula, which extends beyond and back from the scleral spur. The fibers of the meshwork are inserted into a connective tissue layer, which covers the ciliary muscle and is continuous in depth with the septums that divide the muscular bundles. This lamella follows the concave surface of the sinus, from the spur to the root of the iris. It has already been described by other authors (Virchow, Fuchs and Lauber), but the name "trabeculoconnective lamella" given by Busacca is worth keeping, as it calls attention to the relationship of the fibers of the trabecula to the surface of the ciliary body. This is important in pathologic conditions, especially in cases of simple glaucoma.

The clinical chapters of Busacca's book are more important. His description of the various kinds of peripheral synechias (he calls them "goniosynechias") is interesting and throws light on the fission of the anterior mesodermal layer of the iris in cases of certain adhesions. He considers the synechia the result "of an inflammatory process localized on the sinus wall."

In the chapter on glaucoma, he states that gonioscopy has not been able to produce a "pathognomonic sign characteristic of this disease" and expresses the belief that the problem cannot be solved by this method. No one has claimed that the pathogenesis of glaucoma can be elucidated by gonioscopy alone. However, Busacca ignores the results of

hundreds of observations made, in order of sequence, by myself, Werner Sugar and Gradle, Barkan, McLean, Kronfeld and others, which have conclusively shown that there is a great difference in the appearance of the angle in cases of simple glaucoma and in those of the congestive type. We have shown that in cases of the former the angle is almost always open while in cases of the latter the angle is narrow and usually peripheral synechias are present. Busacca, on the contrary, says that in the great number of cases of simple glaucoma he has studied the iridocorneal sinus could be classified as a "narrow sinus" because the "line of the crests" (the most prominent ridge of the iris) was facing the anterior part of the trabecula or the cornea, "giving to the broad slit the impression of a wide sinus on account of the transparency of the corneal tissue." However, he has also observed cases of wide sinuses. In cases of acute congestive glaucoma, he states that the narrow entrance to the sinus has no direct bearing on the glaucomatous attack and that it is not a predisposing cause. This is contrary to the opinion expressed by many authors, from Fuchs to Gradle and Sugar. Busacca still clings to the opinion of Salzmann, who stated the belief that atropine enlarges the chamber sinus and physostigmine narrows it. Sugar has shown that the converse is true.

The chapters on gonioscopy in cases of inflammatory processes of the uvea and of disease of the cornea are well written and informative. I shall mention especially those relating to the gonioscopic aspects after operations on the eyeball and the chapter on congenital malformations of the iris.

The book ends with a chapter on "Experimental Gonioscopy," in which the author studies eyes which have undergone iridectomy for cataract, glaucoma or other diseases. He uses an ocular micrometer attached to the eyepiece of the slit lamp, and with the narrow slit he examines the anterior part of the ciliary body and the ciliary processes visible in the area of the coloboma, noting the number of the processes and their shape, position and dimensions. He then instills atropine or physostigmine into the eye and observes the movements of the heads of the processes. He has seen with use of atropine that the heads retract and the edge of the lens (if it was previously covered) becomes exposed and the sinus shallower. Physostigmine, on the contrary, produces an enlargement of the processes. These cover the margin of the lens, and the entrance to the sinus narrows and becomes deeper.

It is unfortunate that the constant use of new names makes Busacca's descriptions confused and complicated. However, he deserves great credit for his painstaking work and for enlarging and completing the chapter on biomicroscopy of the structures of the angle first undertaken by Bangertner and Goldman.

MANUEL URIBE TRONCOSO

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date

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 Place London Time May 30-June 1-2, 1946

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Place Good Samaritan Hospital, Portland Time Thrd Tuesday of each month

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 Secretary-Treasurer Dr Linley C Happ, 124 Waterman St, Providence
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 second Thursday in October, December, February and April

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 Place University Club, Salt Lake City Time 7 00 p m, third Monday of
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 Secretary Dr Lester A Brown, 815 Doctors Bldg, Atlanta, Ga.
 Place Academy of Medicine Time 7 30 p m, fourth Monday of each month
 from October to May

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 Place Medical and Chirurgical Faculty, 1211 Cathedral St. Time 8 30 p m,
 fourth Thursday of each month from October to March

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Place Tutwiler Hotel Time 6 30 p m, second Tuesday of each month, September to May, inclusive

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Place Kings County Medical Society Bldg, 1313 Bedford Ave Time Third
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Secretary-Treasurer Dr Sheldon B Freeman, 196 Linwood Ave, Buffalo 9
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Place Mountain City Club Time Second Thursday of each month from
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Secretary Dr J R Fitzgerald, 3215 W North Ave, Chicago
Place Continental Hotel, 505 N Michigan Ave Time Third Monday of each
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Secretary Dr A A Levin, 441 Vine St, Cincinnati

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except June, July and August

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Secretary Dr H H Wygand, 624 Guardian Bldg, Cleveland

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Clerk Dr George F J Kelly, 37 S 20th St, Philadelphia

Time Third Thursday of every month from October to April, inclusive

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Place University Club Time 6 15 p m, first Monday of each month, from
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Texas

Secretary Dr F B Kelly, 519 Medical Professional Bldg, Corpus Christi, Texas
Time 6 30 p m, third Tuesday of each month from October to May

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President Dr Spight Jenkins, 1719 Pacific Ave Dallas, Texas
 Secretary Dr L Drough Dallas Medical and Surgical Clinics, Dallas, Texas
 Place Dallas Athletic Club Time 6 30 p m, first Tuesday of each month
 from October to June The November, January and March meetings are
 devoted to clinical work

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President Dr H I McPherrin, 406-6th Ave, Des Moines, Iowa
 Secretary-Treasurer Dr C C Jones, Bankers Trust Bldg, Des Moines, Iowa
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Chairman Members rotate alphabetically
 Secretary Dr Wesley G Reid, 974 Fisher Bldg, Detroit 2
 Place Club rooms of Wayne County Medical Society Time First Monday of
 each month, November to April, inclusive

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 Secretary Dr William S Gonne, 619 David Whitney Bldg, Detroit 26
 Place Club rooms of Wayne County Medical Society Time 6 30 p m, third
 Thursday of each month from November to April, inclusive.

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 Place Medical Hall, Medical Arts Bldg Time 7 30 p m, first Friday of each
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 Secretary Dr John H Barrett, 1304 Walker Ave, Houston, Texas
 Place River Oaks Country Club Time 6 30 p m, second Thursday of each
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 month from November to May

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President Dr Edgar Johnson, 906 Grand Ave, Kansas City, Mo
 Secretary Dr W E Keith, 1103 Grand Ave, Kansas City, Mo
 Time Third Thursday of each month from October to June The November,
 January and March meetings are devoted to clinical work

LONG BEACH EYE, EAR, NOSE AND THROAT SOCIETY

Chairman Dr Francis Carl Hertzog, 117 E 8th St, Long Beach, Calif
 Secretary-Treasurer Dr Robert G Thornburgh, 117 E 8th St, Long Beach, Calif
 Place Seaside Hospital Time Last Wednesday of each month from October to May

LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

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 Secretary-Treasurer Dr K C Brandenburg, 110 Pine Ave, Long Beach 2, Calif
 Place Los Angeles County Medical Association Bldg, 1925 Wilshire Blvd Time
 6 30 p m, fourth Monday of each month from September to May, inclusive

LOUISVILLE EYE AND EAR SOCIETY

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 Secretary-Treasurer Dr J W Fish, 321 W Broadway, Louisville, Ky
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 Secretary Dr James J Monohan, 31 S Jardin St, Shenandoah, Pa

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 Secretary Dr Frazier Williams, 1801 I St N W, Washington
 Place 1718 M St N W Time 8 p m, third Friday of each month from October to April, inclusive

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

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 Secretary Dr Sam H Sanders, 1089 Madison Ave, Memphis, Tenn
 Place Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital Time 8 p m,
 second Tuesday of each month from September to May

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 Secretary-Treasurer Dr Frank G Treskow, 411 E. Mason St, Milwaukee 2
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 Secretary-Treasurer Dr Maitland D Place, 981 Reibold Bldg, Dayton, Ohio
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 Secretary Dr L Tessier, 1230 St Joseph Blvd E, Montreal, Canada
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 Secretary Dr R E Sullivan, 432 Doctors Bldg, Nashville 3, Tenn
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 Secretary Dr Mercer G Lynch, 1018 Maison Blanche Bldg, New Orleans
 Place Louisiana State University Medical Bldg Time 8 p m, second Tuesday
 of each month from October to May

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 Secretary Dr Milton Berliner, 57 W 57th St, New York
 Time 8 30 p m, third Monday of every month from October to May, inclusive

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President Dr Benjamin Friedman, 6 W 77th St, New York
 Secretary Dr Benjamin Esterman, 983 Park Ave, New York 28
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President Dr S R Shaver, 117 N Broadway, Oklahoma City
 Secretary Dr William Mussil, Medical Arts Bldg, Oklahoma City
 Place University Hospital Time Second Tuesday of each month from Sep-
 tember to May

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OTO-LARYNGOLOGICAL SOCIETY

President Dr A A Steinberg, 1502 Farnam St, Omaha
 Secretary-Treasurer Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha 2
 Place Omaha Club, 20th and Douglas Sts, Omaha Time 6 p m dinner, 7 p m
 program, third Wednesday of each month from October to May

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 Secretary-Treasurer Dr J Averbach, 435 Clifton Ave, Clifton, N J
 Place Paterson Eye and Ear Infirmary Time 9 p m, last Friday of every
 month, except June, July and August

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 Secretary Dr Glen Gregory Gibson, 255 S 17th St, Philadelphia
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 to April, inclusive, except December, at 8 00 p m

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 cine, Randolph Field, Texas
 Place San Antonio, Brooke General Hospital, Randolph Field or San Antonio
 Aviation Cadet Center Time 7 p m , second Tuesday of each month from
 October to May

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 EAR, NOSE AND THROAT

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President Dr Clarence A Veasey Sr , 421 W Riverside Ave , Spokane, Wash
 Secretary Dr Clarence A Veasey, 421 W Riverside Ave , Spokane, Wash
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 except June, July and August

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Place Office of chairman Time Last Tuesday of each month from October to May

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